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		*P* value
	ERS (n = 14)	BS with ER (n = 5)	
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.

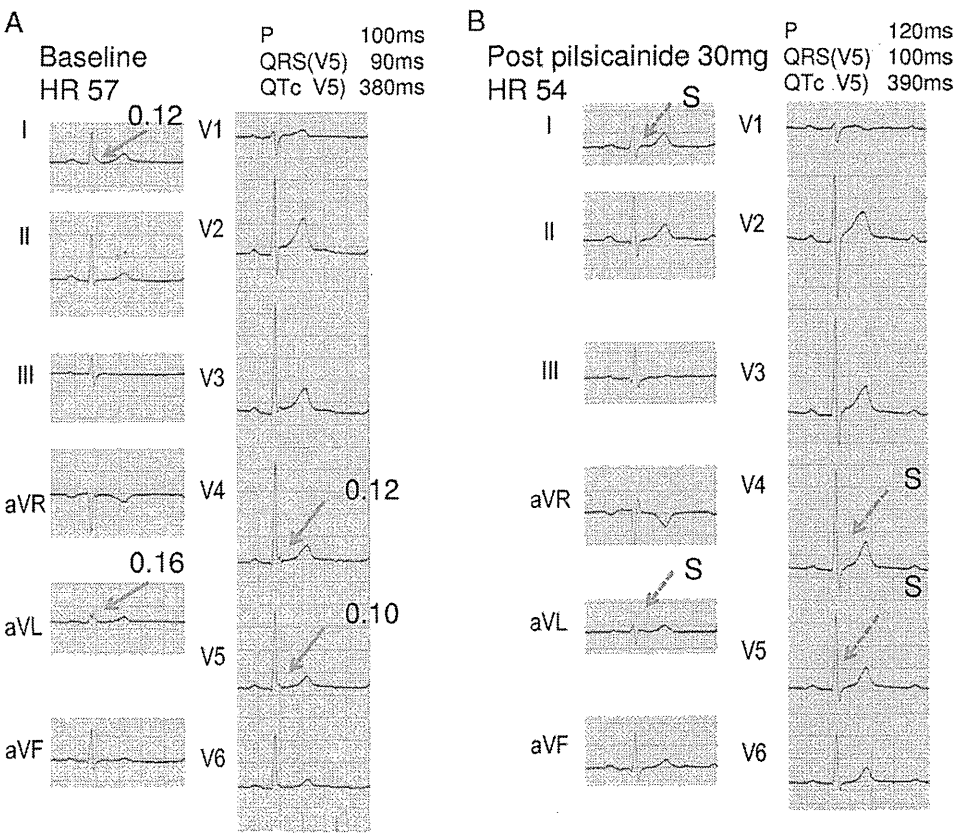

Figure 2 Twelve-lead ECGs in a patient with early repolarization syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the lateral leads (I, aVL, and V4–V5) under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide 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.

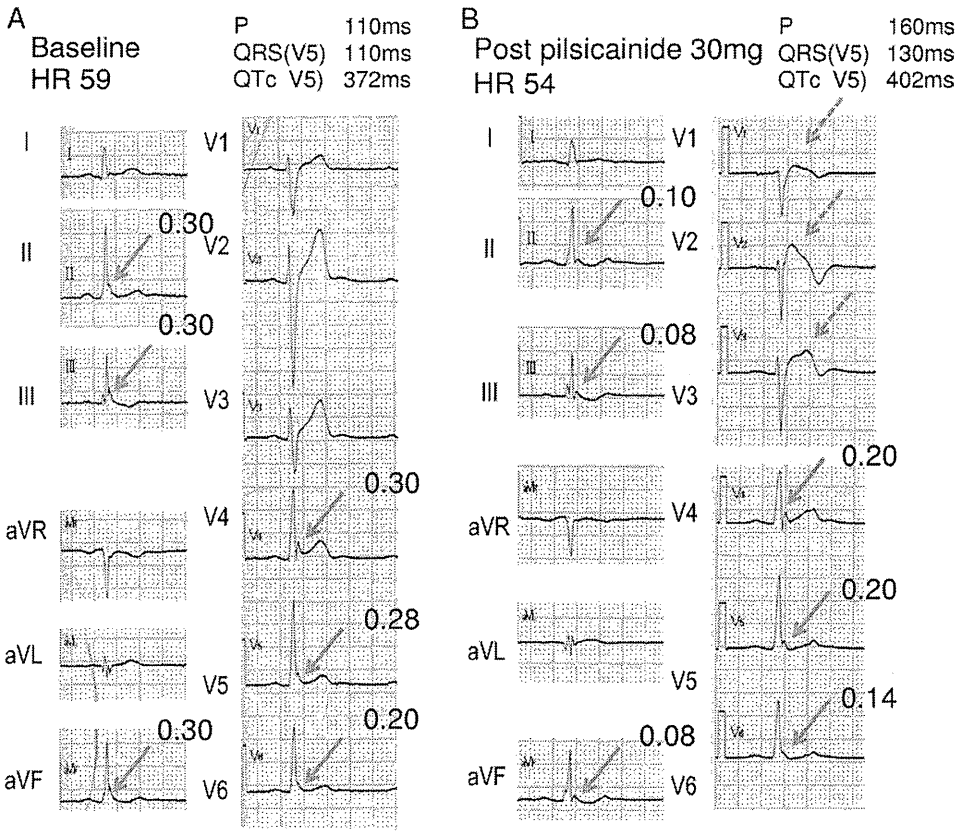

Figure 3 Twelve-lead ECGs in a patient with Brugada syndrome under baseline conditions (**A**) and after pilsicainide administration (**B**). ER was seen in the inferior (II, III, and aVF) and lateral (V4–V6) leads under baseline conditions (**A**, arrows). Intravenous administration of 30 mg of pilsicainide 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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Clinical impact of the number of extrastimuli in programmed electrical stimulation in patients with Brugada type 1 electrocardiogram

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BACKGROUND Use of programmed electrical stimulation (PES) for risk stratification of Brugada syndrome (BrS) is controversial.

OBJECTIVE To elucidate the role of the number of extrastimuli during PES in patients with BrS.

METHODS Consecutive 108 patients with type 1 electrocardiogram (104 men, mean age 46 ± 12 years; 26 with ventricular fibrillation [VF], 40 with syncope, and 42 asymptomatic) underwent PES with a maximum of 3 extrastimuli from the right ventricular apex and the right ventricular outflow tract. Ventricular arrhythmia (VA) was defined as VF or nonsustained polymorphic ventricular tachycardia >15 beats. Patients with VA induced by a single extrastimulus or double extrastimuli were assigned to group SD (Single/Double), by triple extrastimuli to group T (Triple), and the remaining patients to group N.

RESULTS VA was induced in 81 patients (VF in 71 and polymorphic ventricular tachycardia in 10), in 4 by a single extrastimulus, in 41 by double extrastimuli, and in 36 by triple extrastimuli. During 79 ± 48 months of follow-up, 24 patients had VF events. Although the overall inducibility of VA was not associated with an increased risk of VF (log-rank $P = .78$), group SD had worse prognosis than did group T ($P = .004$). Kaplan–Meier analysis in patients without prior VF also showed that group SD had poorer outcome than did group T and group N ($P = .001$). Positive and negative predictive values of VA induction with up to 2 extrastimuli were, respectively, 36% and 87%, better than those with up to 3 (23% and 81%, respectively).

CONCLUSIONS The number of extrastimuli that induced VA served as a prognostic indicator for patients with Brugada type 1 electrocardiogram. Single extrastimulus or double extrastimuli were adequate for PES of patients with BrS.

KEYWORDS Brugada syndrome; Programmed electrical stimulation; Number of extrastimuli; Risk stratification; Sudden death

ABBREVIATIONS **BrS** = Brugada syndrome; **ECG** = electrocardiogram; **ICD** = implantable cardioverter-defibrillator; **LAS40** = duration of low-amplitude signals <40 μV of the filtered QRS complexes; **NPV** = negative predictive value; **PES** = programmed electrical stimulation; **PPV** = positive predictive value; **PVT** = polymorphic ventricular tachycardia; **RVA** = right ventricular apex; **RVOT** = right ventricular outflow tract; **RMS40** = root mean square voltage of the terminal 40 ms of the filtered QRS complexes; **VA** = ventricular arrhythmia; **VF** = ventricular fibrillation

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Introduction

Brugada syndrome (BrS) is a channelopathy that can cause sudden death due to ventricular fibrillation (VF) in apparently healthy individuals in their prime. Since Brugada et al reported it first in 1992, several indices have been reported as reliable prognostic factors.[1–6] However, there remains much room for debate in prognostic indices except for history of VF.[7] Although induction of lethal ventricular

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arrhythmia (VA) by programmed electrical stimulation (PES) is still widely adopted for deciding the indication of an implantable cardioverter-defibrillator (ICD), controversial data have been reported regarding its prognostic value.[2,4,7–9] Brugada et al reported that VF inducibility by PES can be a strong predictor of subsequent cardiac events in patients with BrS.[8] However, other studies could not confirm these findings.[2,4,7] Because protocols of PES and backgrounds of patients were different in each study, direct comparison of the results was not possible. Moreover, clinical significance of the number of extrastimuli, the site of induction, and the coupling interval of extrastimuli at the time of VF induction by consistent protocol have not been fully elucidated.

The aim of the present study was to test the hypothesis that subsequent cardiac events occur more frequently in patients with BrS with induction of VAs by fewer extrastimuli during PES. Thus, we examined the relationships of several parameters of PES, especially the number of extrastimuli, the site of induction, and the coupling interval of extrastimuli at the time of VF induction, with subsequent cardiac events.

Methods

Study population

The study population consisted of consecutive 108 Japanese patients with Brugada type 1 electrocardiogram (ECG) in the absence or presence of sodium-channel–blocking agent (104 men, mean age 46 ± 12 years) who underwent electrophysiological study at National Cerebral and Cardiovascular Center, Suita, Japan, between 1993 and 2009. Twenty-six patients had a history of VF, 40 had a history of syncope, and 42 were asymptomatic at the time of the electrophysiological study. Patients' characteristics are shown in Table 1. Two patients with nocturnal agonal respiration were included in VF patients.

Table 1 Overall clinical and electrocardiographic characteristics of 108 patients

Characteristics	N (%)
Clinical	
Male	104 (96%)
Age (y)	46 ± 12
Hx of VF	26 (24%)
Hx of syncope	40 (37%)
Asymptomatic	42 (39%)
Family Hx of BrS	6 (6%)
Family Hx of SD under age 45 y	22 (20%)
Age at first CE (y)	43 ± 14
Electrocardiographic	
RR interval (ms)	971 ± 118
PQ interval (ms)	176 ± 29
QRS duration (ms)	96 ± 16
Corrected QT interval (ms)	405 ± 29
Spontaneous coved-type ST segment	62 (57%)
Total filtered QRS duration	119 ± 17
LAS40	47 ± 16
RMS40	16 ± 11

BrS = Brugada syndrome; CE = cardiac event; Hx = history; SD = sudden death; VF = ventricular fibrillation.

Brugada type 1 ECG was diagnosed when a coved ST-segment elevation (≥0.2 mV at J point) was observed in more than one of the right precordial leads (V1–V3) in the presence or absence of a sodium-channel–blocking agent. Sixty-two patients exhibited spontaneous type 1 ECG, and the rest of the patients showed type 2 or 3 ECG at baseline and type 1 ECG after administration of 1 mg/kg of pilsicainide. Obvious type 1 ECG (>2 mm J-point elevation followed by >3 mm ST elevation in precordial leads) was confirmed after pilsicainide administration in all patients with drug-induced type 1 ECG. Patients were diagnosed as suffering from BrS according to the report of the second consensus conference.[10]

Clinical information

History taking, physical examinations, chest roentgenogram, and ECG were conducted. All participants underwent echocardiography to exclude structural heart disease. Clinical information including age, sex, family history, and age of first cardiac event was collected. Twelve-lead ECG was recorded in all 108 patients, and the RR interval, PR interval (lead II), QRS duration (lead V5), and corrected QT interval (lead V2) were measured. Signal-averaged ECG was recorded and analyzed in 91 patients by using a signal-averaged ECG system (Arrhythmia Research Technology 1200EPX, Milwaukee, WI). Three parameters were assessed by using a computer algorithm: (1) total filtered QRS duration, (2) root mean square voltage of the terminal 40 ms of the filtered QRS complexes (RMS40), and (3) duration of low-amplitude signals <40 μV of the filtered QRS complexes (LAS40). Late potential was considered positive when the 2 criteria (RMS40 < 18 μV and LAS40 > 38 ms) were fulfilled. Genetic test for the presence of an *SCN5A* mutation was also performed by direct sequencing, and the entire coding sequence of the *SCN5A* gene was thoroughly searched.

Electrophysiological study

An electrophysiological study was conducted in fasting and nonsedated state after written informed consent. None of the patients received antiarrhythmic drugs before the electrophysiological study. The atrio–His and His–ventricular intervals were measured during sinus rhythm. We defined the induction of VA as an induction of VF or nonsustained polymorphic ventricular tachycardia (PVT) of more than 15 consecutive beats. A maximum of 3 programmed ventricular extrastimuli were delivered from the right ventricular apex (RVA) and the right ventricular outflow tract (RVOT), unless VA was induced. First, single extrastimulus and double extrastimuli were delivered from the RVA followed by the RVOT. Next, triple extrastimuli was delivered from the RVA followed by the RVOT. The basic cycle length was 500 ms. The coupling interval was reduced in decrements of 10 ms until ventricular refractoriness, coupling interval reached 180 ms, or VF was induced.

We divided the study subjects into 3 groups according to the results of the PES. Patients with VA induced by a single extrastimulus or double extrastimuli were assigned to group

SD, by triple extrastimuli to group T, and noninducible patients to group N. We also evaluated the significance of the site of induction (the RVA or the RVOT) and the coupling interval of extrastimuli at the time of VA induction (<200 ms or ≥200 ms) on the prognosis of the patients.

Follow-up

An ICD implantation was proposed for all the patients with a previous VF and for those in whom VF or PVT was induced during the electrophysiological study. All patients were followed up in the outpatient clinic. Patients with and without ICD were followed up at every 3 and 6 months, respectively. Primary clinical outcome was determined as an occurrence of VF, sustained ventricular tachycardia, or sudden death.

Statistical analysis

Data were analyzed with JMP 8.0 software package (SAS Institute, Inc, Cary, NC). Numeric values were expressed as mean ± standard deviation. χ^2test, Student's t test, or 1-way analysis of variance was performed when appropriate to test for statistical differences. $P<.05$ was considered statistically significant. Event rate curves were plotted according to the Kaplan–Meier method and were analyzed with the log-rank test. Univariate and multivariate Cox regression were performed to assess predictive values of factors for subsequent cardiac events.

Results

Electrophysiological study

VA was induced in 81 patients (VF in 71 and PVT in 10): in 4 by single extrastimulus, in 41 by double extrastimuli, and in 36 by triple extrastimuli. There were 45 patients in group SD, 36 in group T, and 27 in group N.

Patients' characteristics are presented in Table 2. There were no significant differences among the 3 groups in gender, age, history of VF or syncope, family history of BrS or sudden death under 45 years of age, and age at the first cardiac event. There were also no significant differences in ECG parameters of the RR interval, PQ interval, QRS duration, corrected QT interval, and incidence of *SCN5A* mutation. Spontaneous coved-type ST segment was the only factor with significantly higher incidence in group SD than in group T and group N. LAS40 tended to be longer and RMS40 tended to be smaller in group SD and group T than in group N.

Table 2 Clinical, electrocardiographic, genetic, and electrophysiological characteristics

Characteristics	Group SD (n = 45)	Group T (n = 36)	Group N (n = 27)	*P* value
Clinical				
Male	44 (98%)	34 (94%)	26 (96%)	.73
Age (y)	48 ± 11	45 ± 13	44 ± 14	.31
Hx of VF	11 (24%)	9 (25%)	6 (22%)	.97
Hx of syncope	17 (38%)	13 (36%)	10 (37%)	.99
Asymptomatic	17 (38%)	14 (39%)	11 (41%)	.97
Family Hx of BrS	3 (7%)	0 (0%)	3 (11%)	.15
Family Hx of sudden death under age 45 y	10 (22%)	6 (17%)	6 (22%)	.80
Age at first CE (y)	44 ± 16	43 ± 14	41 ± 13	.86
Electrocardiographic				
RR interval (ms)	978 ± 125	990 ± 112	936 ± 108	.18
PQ interval (ms)	173 ± 27	178 ± 23	181 ± 39	.54
QRS duration (ms)	95 ± 15	99 ± 16	96 ± 19	.63
Corrected QT interval (ms)	404 ± 31	405 ± 26	406 ± 30	.97
Spontaneous coved-type ST segment	32 (71%)	19 (53%)	11 (41%)	.033
Total filtered QRS duration	122 ± 19	119 ± 16	114 ± 14	.17
LAS40	49 ± 16	49 ± 19	41 ± 13	.13
RMS40	14 ± 10	17 ± 10	20 ± 13	.051
Late potential*	32/44 (73%)	25/35 (71%)	13/24 (54%)	.25
Genetic				
SCN5A mutation	6 (13%)	3 (8%)	3 (11%)	.78
Electrophysiological				
AA interval	921 ± 153	903 ± 174	905 ± 143	.86
AH interval	106 ± 31	101 ± 21	108 ± 33	.65
HV interval	45 ± 12	44 ± 8	42 ± 9	.58
Induction of ventricular arrhythmia				
Ventricular fibrillation	40 (89%)	31 (86%)		NA
PVT >15 successive beats	5 (11%)	5 (14%)		NA
Site of induction				
Right ventricular apex	11 (24%)	13 (36%)		NA
Right ventricular outflow tract	34 (76%)	23 (64%)		NA

AH = atrio–His; BrS = Brugada syndrome; CE = cardiac event; HV = His–ventricular; Hx = history; NA = not available; PVT = polymorphic ventricular tachycardia; VF = ventricular fibrillation.

*Late potential was considered present when the 2 criteria (LAS40 > 38 ms and RMS40 < 18 μV) were fulfilled.

As for electrophysiological characteristics, AA, atrio–His, and His–ventricular intervals showed no significant differences among the 3 groups. VA was more frequently induced from the RVOT than from the RVA (57 [70%] vs 24 [30%], respectively).

Subsequent cardiac events during follow-up

We recommended all patients with prior VF episode, group SD patients, and group T patients with prior syncope to undergo an ICD implantation. For asymptomatic group T patients, and group N patients without prior VF, ICD implantation was performed only for those who wanted it after informed consent. Forty-one of the 45 group SD patients (91%), 25 of the 36 group T patients (69%), and 13 of the 27 group N patients (48%) underwent an ICD implantation.

There were no deaths during 82 ± 48 months of follow-up; 24 patients had VF events. All these 24 patients had undergone ICD implantation, and VF was documented on the recordings of the ICD. No patients without ICD experienced any syncope. There were no significant differences in the follow-up period among the 3 groups (group SD 83 ± 50 months, group T 81 ± 44, and group N 80 ± 49; P = .96). Significantly more VF episodes occurred in group SD (16 of 45 [36%]) than in group T (3 of 36 [8%]) and in group N (5 of 27 [19%]) (P = .012).

Figure 1 shows the results of the Kaplan–Meier analysis of subsequent cardiac events. As previously reported, induction of VA was not associated with subsequent cardiac events (Figure 1A, log-rank, P = .78). When we focused on the numbers of extrastimuli, group SD had a significantly higher risk of subsequent cardiac events than did group T (log-rank, P = .004), but there were no significant differences in the subsequent cardiac event rate between group SD and group N and between group T and group N (Figure 1B). Among 82 patients without prior VF episode, VA induction with up to 2 extrastimuli was a significant risk factor of subsequent cardiac events (Figure 1C, log-rank, P = .003).

In 81 patients with induced VA, the site of induction (the RVA or the RVOT) and the coupling interval of extrastimuli at the time of VA induction (<200 ms or ≥200 ms) were not associated with subsequent cardiac events (Figures 2A and 2B, log-rank, P = .57 and .52, respectively). The cardiac event rate was associated with the number of extrastimuli, not with the site of induction and the coupling interval (Figures 3A and 3B).

As for 42 asymptomatic patients, 2 of the 17 patients in group SD experienced subsequent VF episodes, whereas none of the 14 patients in group T and 11 in group N experienced subsequent cardiac events. Although the number of patients was small, group SD showed a significantly higher cardiac event rate than did group T and group N (log-rank, P = .046).

Predictors of long-term prognosis

The results of Cox regression analysis are shown in Table 3. In univariate Cox regression, history of VF, VA induced with up to 2 extrastimuli, incidence of spontaneous coved-type ST segment, and Late potential were significant predictors of subsequent cardiac events. Multivariate Cox re-

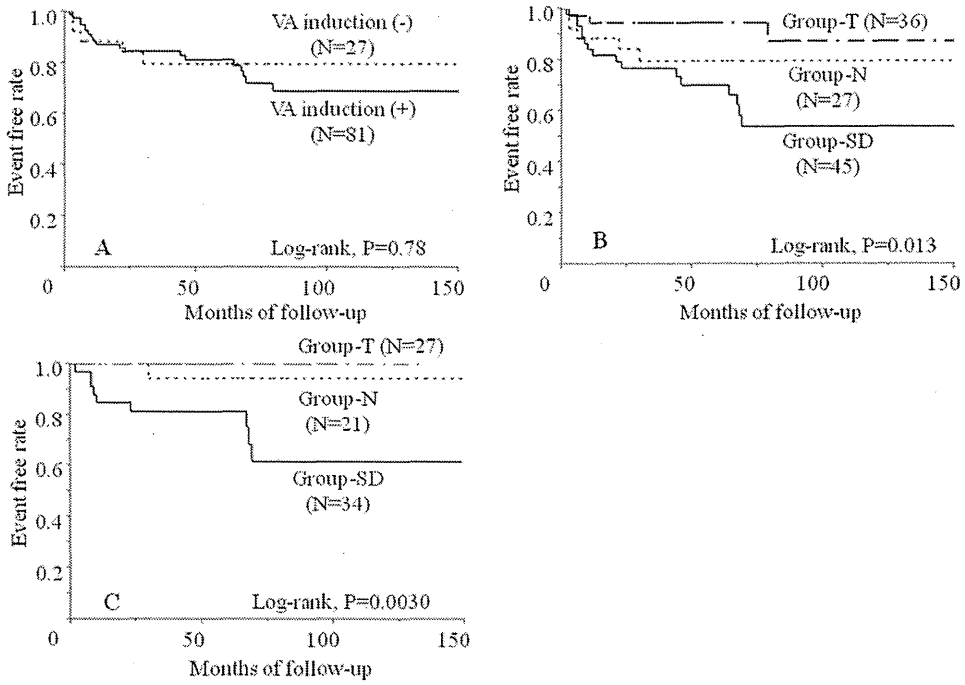

Figure 1 Kaplan–Meier curves of subsequent cardiac events during follow-up. Kaplan–Meier curves of cardiac events (**A**) depending on the overall inducibility of ventricular arrhythmias (VFs and polymorphic ventricular tachycardia >15 successive beats) by up to triple extrastimuli, (**B**) in the 3 groups, and (**C**) in the population of patients without history of VF depending on the 3 groups. Although the overall inducibility was not associated with subsequent cardiac events, inducibility by up to 2 extrastimuli had significant predictive values for the occurrence of subsequent cardiac events. Group SD had a significantly higher cardiac event rate than did group T. In the population of patients without previous VF, inducibility by up to 2 extrastimuli was strongly associated with subsequent cardiac events.

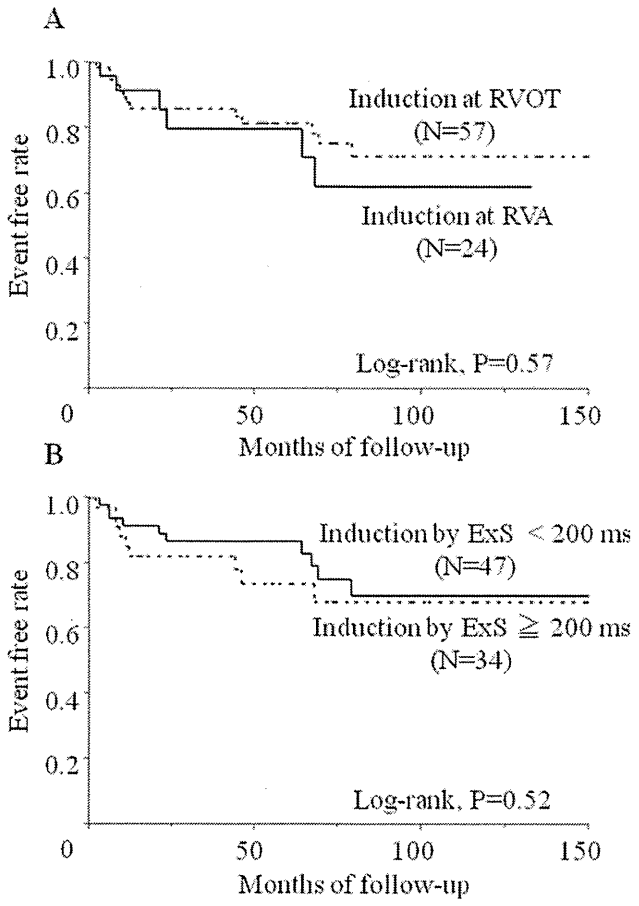

Figure 2 Kaplan–Meier curves of subsequent cardiac events during follow-up. Kaplan–Meier curves of cardiac events (**A**) depending on the induction site and (**B**) the minimum coupling interval of extrastimuli at the time of induction. Neither the site of induction, the right ventricular outflow tract or the right ventricular apex, nor the minimum coupling interval, longer or shorter than 200 ms, was associated with subsequent cardiac events.

gression demonstrated that the only predictive index was VA induction with up to 2 extrastimuli except for history of VF. Neither VA induction from the RVA nor the coupling interval of extrastimuli <200 ms at the time of VA induction was a predictor of subsequent cardiac events.

Discussion

The major findings of the present study were the following: (1) induction of VA by triple extrastimuli was not associated with a higher incidence of subsequent VF, (2) patients with VA induced by up to 2 extrastimuli had significantly more frequent VF episodes during 7 years of follow-up, (3) neither the site of VA induction (the RVA or the RVOT) nor the coupling interval of VA induction (<200 ms or ≥200 ms) was associated with the incidence of subsequent cardiac events.

We evaluated the prognostic role of VA induction by PES and found that the number of extrastimuli that induced VA was prognostic for patients with Brugada type 1 ECG.

Clinical significance of PES in patients with BrS

Conflicting data have been reported from several registries as to the prognostic value of PES in patients with BrS.[4,6,7] Brugada et al reported that PES was a good predictor of arrhythmic events. Meanwhile, Priori et al and Probst et al argued that it was not a useful index. Meta-analysis data indicated that PES was not useful for predicting subsequent cardiac events, and the published ACC/AHA/ESC guidelines referred to PES as a class IIb indication in asymptomatic patients with BrS for risk stratification.[11–13] However, there were several limitations for each registry such as the different PES protocols.[14] Moreover, these conflicting data may be related to the specific inclusion criteria of each registry. Recently, Giustetto et al[9] reported that PES protocol up to 2 extrastimuli with ventricular effective refractory period was useful in risk stratification in patients with BrS. This Italian study agrees with our result that VA induction with up to 2 extrastimuli could help predict subsequent cardiac events if a consistent PES protocol is used. The present study also demonstrated that a PES protocol with up to 3 extrastimuli was not useful for risk stratification in patients with BrS. We presume that this result in part explains why several registries reported conflicting data.

Patients without VA induction, especially patients with history of VF, had subsequent arrhythmic events in the present study (5 of 27 [19%]). In this respect, the present study differs from the Italian study. We can cite 2 contributing factors. First, our follow-up period was nearly 7 years, which was much longer than that of the Italian study. Second, we adopted only 1 basic cycle length, whereas Giustetto et al adopted 2 basic cycle lengths; hence, it is possible that we could not induce VA in some patients.

Underlying mechanism

Arrhythmogenicity in patients with BrS is possibly associated with both repolarization and depolarization abnormal-

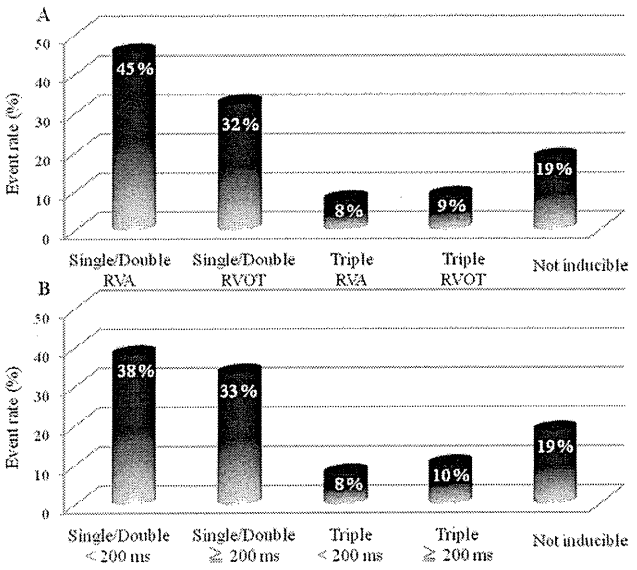

Figure 3 Incidence of subsequent cardiac events according to the number of extrastimuli, the site of induction, and the minimum coupling interval at the time of induction. Incidence of cardiac events (**A**) according to the number of extrastimuli and the site of induction and (**B**) the number of extrastimuli and the minimum coupling interval. The patients whose ventricular arrhythmias were induced by up to 2 extrastimuli had a higher incidence of cardiac events in both categories.

Table 3 Predictive factors of subsequent cardiac events

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Hx of VF	4.59 (2.05–10.7)	<.001	3.47 (1.50–8.27)	.004
VA induced with double extrastimuli	3.21 (1.41–7.92)	.005	3.03 (1.26–8.00)	.013
Spontaneous coved-type ST segment	3.20 (1.28–9.65)	.011	1.77 (0.67–5.56)	.26
Late potential	2.72 (1.02–9.40)	.046	1.77 (0.60–5.98)	.34
SCN5A mutation	2.92 (0.96–7.33)	.057	1.66 (0.47–4.63)	.40
VA induction at the RVA	1.29 (0.47–3.07)	.60		
VA induced with CI < 200 ms	0.86 (0.37–1.91)	.71		
VA induced by PES	1.21 (0.48–3.64)	.71		
Family Hx of sudden death under age 45	1.18 (0.39–2.95)	.74		

CI = coupling interval; Hx = history; PES = programmed electrical stimulation; RVA = right ventricular apex; VA = ventricular arrhythmia; VF = ventricular fibrillation. Parentheses represent 95% confidence interval.

ities. In the present study, patients with induced VA had longer LAS40 (49±17 vs 41±13; $P = .042$) and smaller RMS40 (15±10 vs 20±13; $P = 0.034$) than did noninduced patients, which may reflect depolarization abnormality and is concordant with our previous report.[15]

There have been several reports regarding depolarization abnormalities in BrS such as *SCN5A* mutation or fragmented QRS.[16–18] By using an experimental model, Aiba et al[19] showed that depolarization abnormalities played a significant role in VF maintenance. Thus, if PES results reflect depolarization abnormality, we could evaluate how easily VF continues through PES. The initiation of VF is thought to be due to phase 2 reentry-induced premature beats (repolarization abnormality).[19,20] It could be difficult to evaluate repolarization abnormality through PES, and this is why PES in BrS cannot completely predict subsequent cardiac events.

Clinical implication

According to the ACC/AHA/ESC guidelines, patients with BrS with spontaneous ST-segment elevation and syncope are a class IIa indication for ICD implantation.[13] However, some patients with BrS experience neurally mediated syncope, as previously reported, which should be distinguished from syncope of unknown origin.[21] Therefore, only the history of syncope could lead to unnecessary use of ICD. We showed that PES of up to 2 extrastimuli can predict subsequent events of patients with prior syncope, demonstrating the possibility that PES could help reduce the unnecessary use of ICD in those patients (Figure 1C).

Meta-analysis studies of patients with BrS could not identify a significant role of PES for predicting subsequent arrhythmic events.[11,12] However, many registries included in their meta-analysis adopted PES protocol of up to 3 extrastimuli. Triple extrastimuli could induce VA even in normal individuals and exaggerate nonspecific depolarization abnormality leading to induction of nonspecific VA. This suggests that VA induction by triple extrastimuli may be highly unnatural, resulting in false-positive VA induction.

ACC/AHA/ESC guidelines have not yet delineated an appropriate PES protocol in detail, such as the number of extrastimuli. We showed that single extrastimulus or double extrastimuli are adequate for PES for patients with BrS. Although the number of patients was small, VA induction with up to 2 extrastimuli was associated with subsequent arrhythmic events even in asymptomatic patients. Positive and negative predictive values according to PES protocols are shown in Table 4. Based on our criteria that VA induction was considered positive when VF or PVT with more than 15 successive beats was elicited, a protocol of up to 2 extrastimuli showed that the positive predictive value (PPV) was 36% and the negative predictive value (NPV) was 87%. On the other hand, a protocol of up to 3 extrastimuli showed that PPV was 23% and NPV was 81%. Even when we consider only VF as an induction criterion, both PPV and NPV were higher with up to 2 extrastimuli (Table 4). Based on our data, protocols up to 2 extrastimuli were sufficient for PES in patients with BrS. In the subgroup of 82 patients without prior VF or aborted cardiac arrest, VF occurred in 9 of the 34 patients with VA induced by up to 2 extrastimuli. No VF occurred in 27 patients with VA induced by triple extrastimuli, and only 1 of the 21 noninducible patients experienced VF. The PPV of PES protocol up to 2 extrastimuli was 26%, but the NPV was high at 98%. However, a low PPV of PES can cause unnecessary use of ICD implantation, especially for asymptomatic patients. We still need to make a decision based on several indices combined, as Delise et al[22] have recently reported.

Table 4 Positive and negative predictive values according to protocols of PES

Protocols	PPV	NPV
VF and NSPVT >15 successive beats		
PES with up to 2 ExS	16/45 (36%)	55/63 (87%)
PES with up to 3 ExS	19/81 (23%)	22/27 (81%)
Only VF		
PES with up to 2 ExS	13/40 (33%)	57/68 (84%)
PES with up to 3 ExS	16/71 (23%)	29/37 (78%)

ExS = extrastimuli; NPV = negative predictive value; NSPVT = nonsustained polymorphic ventricular tachycardia; PES = programmed electrical stimulation; PPV = positive predictive value; VF = ventricular fibrillation.

Study limitations

This study has several limitations. First, this was a retrospective study. However, we believe that our data have validity because this was not an interventional study but an observational study, and moreover, the follow-up periods of the 3 groups were not significantly different. Second, this study consisted of a small population of 108 patients, insufficient to fully evaluate the prognosis of patients with BrS. Further study with a larger number of patients with BrS and with consistent protocol of PES will be required to draw a firm conclusion on the importance of the number of extrastimuli. If each registry does not have a large enough number of patients, a meta-analysis that can compare the numbers of extrastimuli could validate the significance of PES. Third, we could have underestimated the cardiac event rate because the end point of the patients without ICD was based on symptoms (syncope); thus, asymptomatic cardiac events during sleep could be missed. Fourth, we adopted only 500 ms as a basic cycle length, and so VA could not be induced in some patients in the present study because this was shorter than in other studies that employed more than 2 basic cycle lengths. However, VA was induced in 75% and VF was induced in 68% of the patients. This induction rate was comparable to that in other registries; this suggests that a single basic cycle length of 500 ms is enough to induce VA. We did not deliver extrastimuli coupled with intervals shorter than 180 ms. Therefore, we could not assess the significance of delivering extrastimuli with intervals shorter than 180 ms. However, extra stimulus with shorter intervals may exaggerate nonspecific depolarization abnormality, leading to induction of nonspecific VA. This issue needs to be addressed. Fifth, the incidence of *SCN5A* mutation was relatively low at 11%, even though we searched the entire coding sequence of *SCN5A*. As previously pointed out, the incidence of *SCN5A* in Japan is lower than in Western countries, and so this study agrees with previous data.[23,24] Finally, there were 46 patients (7 with prior VF, 21 with prior syncope, and 18 asymptomatic) with drug-induced type 1 ECG, which can be misdiagnosed as BrS because of its false-positive ECG morphology. However, the percentage of these patients was lower than that in the FINGER study, and we confirmed the obvious coved ST elevation induced by sodium-channel–blocker test in patients with type 2 and type 3 ECG.

Conclusion

The number of extrastimuli in PES that induced ventricular arrhythmias served as a prognostic indicator for patients with type 1 Brugada ECG. The site of induction and the coupling interval of extrastimuli at the time of VF induction were not prognostic indicators of patients with BrS. Our data suggest that PES in patients with type 1 Brugada ECG should employ up to 2 extrastimuli, rather than 3.

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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. (*Circ J* 2012; **76:** 469–476)

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

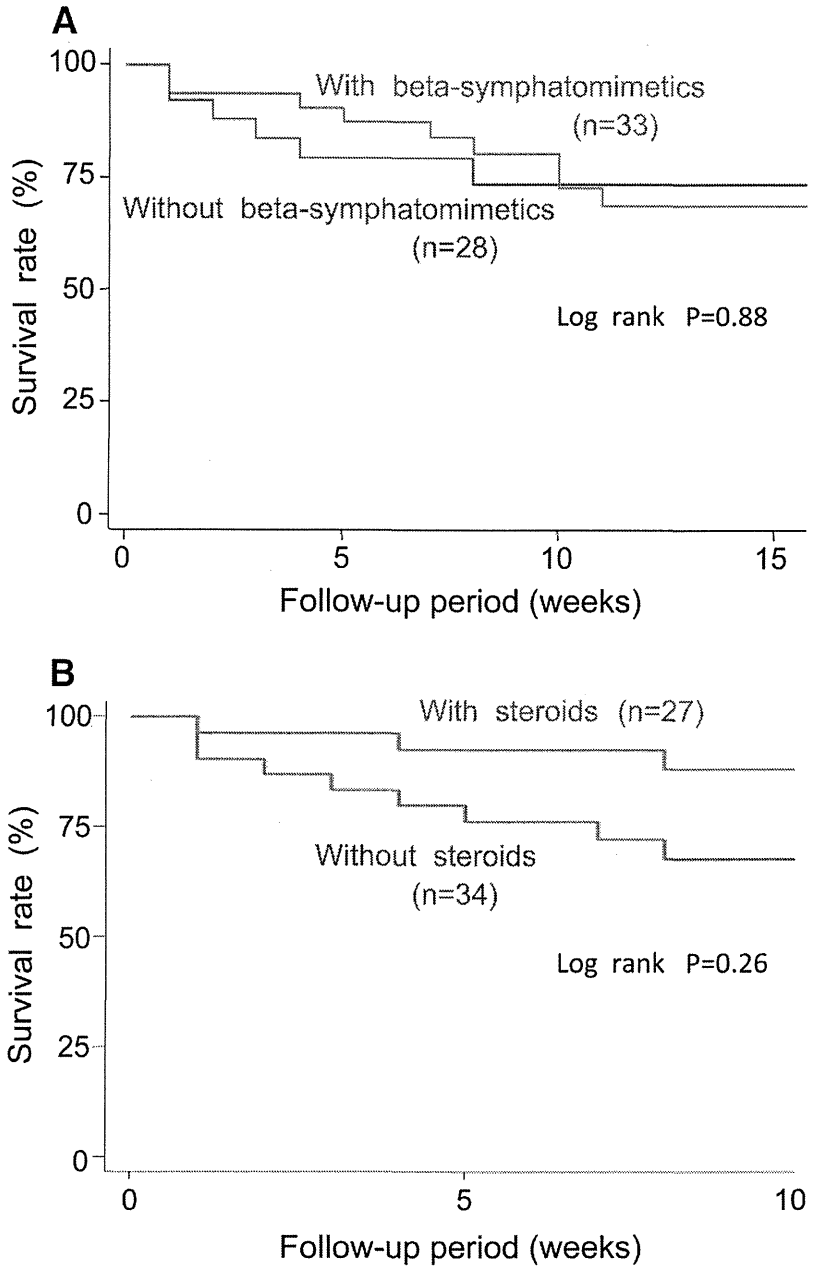

Figure. Kaplan-Meier survival curves (log-rank test and Cox proportional hazard model) for the primary endpoint (fetal death or neonatal death) in fetuses treated (A) with and without β-sympathomimetics and (B) with and without steroids. Follow-up period, time from diagnosis in utero to fetal or neonatal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