Table 1
Clinical characteristics and the results of ventricular stimulation study.

No	Age	Sex	Symptom	FH	Order in drug	Control		ISP		BB	
						Induction	Pacing site	Induction	Pacing site	Induction	Pacing site
1	51	M	1	0	C→ ISP	Positive	RVA	Positive	RVA	–	
2	37	M	0	1	C→ ISP	Positive	RVOT	Positive	RVOT	–	
3	52	M	0	0	C→ ISP	Positive	RVA	Positive	RVA	–	
4	40	M	0	1	C→ ISP	Positive	RVOT	Negative#		–	
5	30	M	1	0	C→ ISP	Positive	RVOT	Negative#		–	
6	50	M	2	0	C→ ISP	Positive	RVA	Negative		–	
7	68	M	1	0	C→ ISP	Positive	RVA	Negative		–	
8	63	M	1	0	C→ ISP	Positive	RVA	Negative		–	
9	57	M	1	0	C→ ISP	Positive	RVA	Negative		–	
10	53	M	1	0	C→ ISP	Positive	RVOT	Negative		–	
11	62	M	1	0	C→ ISP	Positive	RVOT	Negative		–	
12	25	M	1	1	C→ ISP	Positive	RVOT	Negative		–	
13	26	M	0	0	C→ ISP	Positive	RVOT	Negative		–	
14	37	M	0	1	C→ ISP	Positive	RVOT	Negative		–	
15	46	M	0	0	C→ ISP	Positive	RVOT	Negative		–	
16	39	M	0	0	C→ ISP	Positive	RVOT	Negative		–	
17	55	M	2	1	C→ ISP→ PRO	Positive	RVA	Negative		Positive	RVOT
18	28	M	2	0	C→ ISP→ PRO	Positive	RVOT	Negative		Positive	RVOT
19	59	M	1	0	C→ ISP→ PRO	Positive	RVOT	Negative		Positive	RVOT
20	62	M	0	0	C→ ISP→ PRO	Positive	RVOT	Negative		Negative	
21	62	M	0	0	C→ ISP→ PRO	Positive	RVA	Negative		Positive	RVA
22	62	M	0	0	C→ ISP→ PRO	Positive	RVOT	Negative		Positive	RVA
23	77	M	1	0	C→ BB→ ISP	Positive	RVA	Positive	RVOT	Positive	RVA
24	71	M	0	1	C→ BB→ ISP	Positive	RVA	Positive	RVA	Positive	RVA
25	54	M	0	0	C→ BB→ ISP	Positive	RVA	Negative		Positive	RVOT
26	48	M	1	0	C→ BB	Positive	RVA	–		Positive	RVOT
27	50	M	0	0	C→ BB	Positive	RVOT	–		Positive	RVOT

M, male; FH, family history of sudden cardiac death; ISP, isoproterenolol; PRO, administration of propranolol (i.v.); C, control; RVA, right ventricular apex; RVOT, right ventricular outflow tract, –, not done; #, non-sustained polymorphic ventricular tachycardia was induced.

fulfilled the following study criteria were selected: (1) diagnosis of BS; (2) VF > 10 s induced from 2 right ventricular sites [right ventricular apex (RVA) and/or right ventricular outflow tract (RVOT)] in the control state; (3) electrophysiological stimulation (EPS) also performed during administration of ISP and/or after intravenous injection of PRO. In this study, symptomatic was defined as patients with a history of documented ventricular tachycardia (VT), VF, or a history of syncope, and asymptomatic was defined as patients without episodes of documented lethal ventricular arrhythmia and/or syncope.

In addition, patients had undergone ECG, Na^+ channel blocker challenge testing, coronary angiography, and cardiac echocardiography during their hospitalization (Table 1).

Diagnosis of BS was based on criteria from a previous report [16] as follows: type 1 ECG shown spontaneously or in response to Na^+ channel blocker challenge testing in the standard right precordial leads (leads V1–3) or one intercostal space above the standard right precordial leads, and absence of other factors such as ischemia, electrolyte disturbance, or hypothermia that may cause ST-segment abnormality. All patients underwent echocardiography with careful attention to RV enlargement and/or wall motion abnormalities to exclude arrhythmogenic RV cardiomyopathy. Implantable cardioverter–defibrillators were implanted in 3 patients in the asymptomatic group and 9 patients in the symptomatic group.

Patients provided written informed consent. This study was approved by the Institutional Clinical Research and Ethics Committee of Yamaguchi Graduate School of Medicine.

Na^+ channel blocker challenge testing

Na^+ channel blocker challenge testing was performed using pilsicainide, as previously reported [16]. The so-called "pure Na^+ channel blocker" pilsicainide was administered intravenously at 1 mg/kg for 10 min with continuous ECG and non-invasive blood pressure monitoring. During drug administration, we started monitoring not only the standard right precordial leads V1–3, but also those recorded from 1 intercostal space higher than the right precordial leads using the V4–6 electrodes. Drug administration was immediately stopped when ST elevation (>0.5 mV), extensive QRS prolongation, unfavorable symptoms, and/or frequent ventricular arrhythmias were observed. The test was considered positive if the coved-type ECG pattern (type 1 ECG) appeared in more than one right precordial lead. Further, the additional ST elevation more than 1 mm was positive when the patient had already type 1 ECG immediately before Na^+ channel blocker challenge testing.

Electrophysiological testing

EPS was performed as reported previously [17,18]. Patients underwent testing in the fasting state. All previous anti-arrhythmic agents had been discontinued for at least five half-lives. An intravenous propofol infusion was used to achieve general anesthesia.

Recordings

A standard 6F decapolar catheter with 2-mm-wide electrodes and 2-mm interelectrode spacing were positioned in the high lateral right atrium, His bundle region, coronary sinus, RVA, and RVOT. The 12-lead surface ECG leads were recorded through a 0.5–100-Hz filter. ECG was recorded simultaneously with intracardiac electrograms (ICEs). Bipolar endocardial electrograms were recorded through a 30–150 Hz filter with a sampling interval of 1 kHz using a computed electric recorder (CardioLAB v51D, GE Medical Systems, Waukesha, WI, USA).

Stimulation protocol

Programmed electrical stimulation was delivered at twice the diastolic threshold at a pulse width of 2 ms (Fukuda-denshi, Tokyo, Japan). Programmed stimulation at basic cycle lengths of 600 and 400 ms at the RVA pacing site started with up to 2 extrastimuli and

a minimum coupling interval of S_2S_3 180 ms. The same method was used at the RVOT pacing site. Then, programmed stimulation with 3 extrastimuli and minimum coupling intervals of S_2S_3 and S_3S_4 200 ms and rapid pacing down to a cycle length of 240 ms or 2:1 ventricular response were performed at the RVA site. Finally, the same method was used at the RVOT pacing site. When VF was induced during pacing, cardioversion therapy was initiated after observation for several seconds to confirm lack of spontaneous termination. Direct current (DC) shock was then delivered. Stimulation resumed 5 min after successful cardioversion in all induced VF. In only one VF episode, cardioversion was not performed because VF terminated spontaneously at 15.8 s immediately before the delivery of DC.

ISP and PRO administration

After examination of the control state, ISP was administered as a bolus injection intravenously at a dose of 1–2 μg, followed by continuous ISP infusion at a dose of 0.15–0.30 μg/min until baseline heart rate increased 20 bpm, at which point EPS was begun. Sixteen patients received ISP alone (case no. 1–16 in Table 1). In 6 patients, PRO (total dose: 0.1 mg/kg) was injected intravenously at 1 mg/min after EPS under ISP, and EPS was restarted (case no. 17–22 in Table 1). In 3 patients, EPS during ISP was performed after EPS of PRO (case no. 23–25 in Table 1). In 2 patients, EPS was performed in the control state and after the administration of PRO (case no. 26–27 in Table 1).

We measured heart rate just before EPS in the control state and ISP, and then calculated the increased rate of the heart rate (%), (the difference of the heart rate before EPS between control state and ISP/the heart rate in control) × 100, to assess the effect of ISP.

In the present study, VF was defined as a fast irregular ventricular rhythm with a continuously changing morphology and a cycle length <200 ms [19] lasting >10 s. A fast irregular ventricular rhythm with a continuously changing morphology and a cycle length >200 ms for >10 s was defined as non-sustained polymorphic VT, but not induced VF. VF duration was calculated from the last stimulation to the last beat of VF.

Signal processing and FFT analysis

The data were analyzed using previously reported methods [13]. In brief, VF episodes were selected using CardioLAB, then transferred to a hard disk. Next, binary data from the ventricular electrogram were retrieved from the hard disk of the CardioLAB system using a USB and made compatible with multipurpose physio-informatic analysis software (BIMUTAS II for Windows, KISSEI COMTEC, Ltd., Tokyo, Japan) on a personal computer. Finally, 5 phases of 4-s data were selected as an epoch (Fig. 1A). Surface ECG (leads I, aVF, V1, and V5) and rectified bipolar electrograms ($RVOT_{distal}$, $RVOT_{proximal}$, RVA_{distal}, and $RVA_{proximal}$) were analyzed using 4096-point FFT (spectral resolution: 0.24 Hz) with a Hamming window [13] and the BIMUTAS II. Each of the four surface ECGs and four ICEs in each epoch was padded to 4096 points with zeros. Further, data in the last phase >2.0 s with 0-padding was formed to 4096 points for FFT analysis in 4 patients.

The power spectrum of electrograms at each recording site was obtained, then the dominant frequency (DF) [11–13], defined as the frequency of the peak with the largest amplitude, was obtained from each epoch in each phase. We also assessed DF from surface ECGs to compare with the DF from bipolar electrograms.

Average DF from surface ECGs and ICEs was calculated to allow quantitative comparison. These values were used as the DF of ECG (DF_{ECG}) and the DF of ICE (DF_{ICE}) in each phase (Fig. 1B).

The effective refractory period (ERP) was defined as the maximum coupling interval during a single program stimulation with a failed ventricular reaction.

Statistical analysis

Data are presented as mean ± SD. A simple regression test was used to determine the relationships among the data. One-factor ANOVA was used for the change of phase analysis. Repeated-measure ANOVA was used to analyze differences in the change of phase between the asymptomatic and symptomatic groups. The chi-square test for independence was used for comparisons of prevalence. Student's *t*-test (unpaired or paired) was also used as appropriate. These analyses were performed using StatView 5.0 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

ERPs and inducibility in controls, ISP, and PRO

ISP significantly shortened the ERP in both the RVA and RVOT at basic cycle lengths of 600 and 400 ms (Table 2). However, there was no significant difference in ERP in either the RVA or RVOT at cycle lengths of 600 and 400 ms for PRO (Table 2).

The mean VF duration was 14.6 ± 2.0 s in the control study (n = 27), 14.5 ± 1.5 s in the ISP study (n = 5), and 14.5 ± 2.1 s in the PRO study (n = 10). ISP decreased the incidence of induced VF from 22 patients to 3 patients (13.6%). Thus, ISP prevented VF induction in 19 patients (86.4%), including 2 patients with non-sustained polymorphic VT (Fig. 2). ISP also suppressed VF in 1 (33.3%) of 3 patients who tested positive after PRO (Fig. 3 and Table 1).

ISP significantly (p < 0.0001) increased the heat rate just before EPS from control state (64.9 ± 9.5 beats/min) to ISP (86.1 ± 14.2 beats/min). There was no significant difference of heart rate just before EPS in the control state between the negative VF group (65.6 ± 9.7 beats/min) and the positive VF group (62.4 ± 9.7 beats/min). Neither, there was no significant difference (p = 0.083) of the heart rate just before EPS in ISP between the negative VF group (88.7 ± 13.6 beats/min) and the positive VF group (75.6 ± 12.6 beats/min). There was a significant difference (p = 0.009) of the increase rate of the heart rate between the negative VF group during EPS in ISP (20.9% ± 4.6%) and the positive VF group during EPS in ISP (37.3% ± 24.0%).

On the other hand, PRO did not change the incidence of induced VF in the 5 patients. In some patients (Fig. 4), ventricular fibrillation was induced in a lower stimulation mode, and surface ECG during VF was disorganized compared with that in the control state. PRO also induced VF in 5 (83.3%) of 6 patients who tested negative after ISP (Fig. 3 and Table 1).

DF transition of VF with phase in the control state

In the control state (n = 27), the duration of induced VF was 14.6 ± 2.0 s. DF_{ECG} significantly increased with phase (p < 0.0001, one-factor ANOVA; 5.61 ± 0.40 Hz, 5.74 ± 0.53 Hz, 6.07 ± 0.36 Hz, 6.13 ± 0.52 Hz, and 6.14 ± 0.50 Hz in phases 1, 2, 3, 4, and 5, respectively; Fig. 5, left panel). DF_{ICE} also significantly increased with phase (p = 0.0006, one-factor ANOVA; 5.72 ± 0.38 Hz, 5.88 ± 0.43 Hz, 6.05 ± 0.37 Hz, 6.14 ± 0.48 Hz, and 6.18 ± 0.51 Hz in phases 1, 2, 3, 4, and 5, respectively; Fig. 5, right panel).

DF transition with phase during ISP

VF was induced in only 5 patients during ISP. In the corresponding cases (n = 5), DF_{ECG} in the control state was 5.63 ± 0.32 Hz, 5.89 ± 0.30 Hz, 6.07 ± 0.36 Hz, 6.13 ± 0.33 Hz, and 6.18 ± 0.39 Hz in phases 1, 2, 3, 4, and 5, respectively. DF_{ECG} during ISP was 5.84 ± 0.13 Hz, 6.12 ± 0.17 Hz, 6.27 ± 0.11 Hz, 6.17 ± 0.19 Hz, and

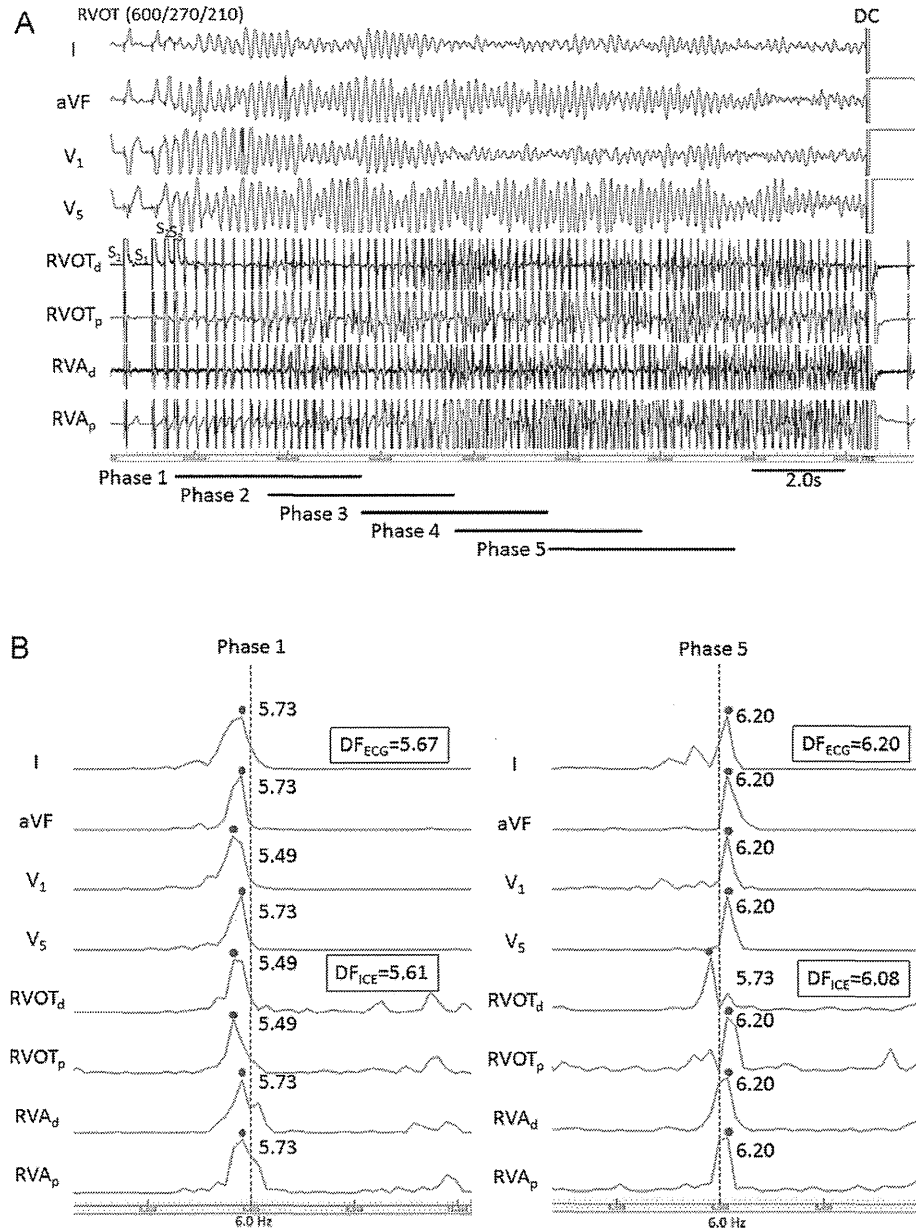

Fig. 1. (A) Representative case of induced ventricular fibrillation (VF) in the control state. Surface electrocardiogram and intracardiac electrogram in a patient with symptomatic Brugada syndrome (case 5, Table 1). VF was induced by double-mode ventricular stimulation ($S_1/S_2/S_3 = 600/270/210$ ms) from the right ventricular outflow tract (RVOT) site. Phase number indicates the 4-s data segment. (B) A Fast Fourier transform (FFT) analysis as in Fig. 2A. Raw data of FFT analysis in phase 1 (left panel) and phase 5 (right panel) are shown. The dominant frequency (DF) is indicated by the number, and the dot represents the maximum point in the power spectrum. DF of ECG (DF_{ECG}) was calculated as the mean DF (in leads I, aVF, V, and V5). The DF of intracardiac ECG (DF_{ICE}) was calculated as the mean DF (in RVOTd, RVOTp, RVAd, and RVAp). Both DF_{ECG} and DF_{ICE} in phase 5 were higher than those in phase 1. The dotted line marks 6.0 Hz. DC, direct current shock delivery; RVAd, the distal pair of the right ventricular apex; RVAp, the proximal pair of the right ventricular apex; RVOTd, the distal pair of the right ventricular outflow tract; RVOTp, the proximal pair of the right ventricular outflow tract.

Table 2
Effective refractory periods of basic cycle lengths of 600 and 400 ms in the control state, isoproterenol (ISP), and propranolol (PRO).

	Control vs. ISP	Control vs. PRO
BCL 600 ms		
RVA (ms)	234 ± 15 vs. 226 ± 13, $n = 16$, $p = 0.034$	238 ± 17 vs. 236 ± 9, $n = 11$, $p = 0.749$
RVOT (ms)	230 ± 12 vs. 219 ± 14, $n = 16$, $p = 0.029$	236 ± 13 vs. 232 ± 12, $n = 11$, $p = 0.309$
BCL 400 ms		
RVA (ms)	213 ± 11 vs. 203 ± 12, $n = 25$, $p = 0.001$	213 ± 14 vs. 215 ± 13, $n = 11$, $p = 0.391$
RVOT (ms)	220 ± 17 vs. 203 ± 16, $n = 25$, $p = 0.002$	219 ± 10 vs. 216 ± 12, $n = 11$, $p = 0.343$

Comparison of the control state with ISP or PRO was performed only in corresponding data.
BCL, basic cycle length; ISP, isoproterenol; PRO, propranolol. ISP significantly shortened the effective refractory period in both the right ventricular apex (RVA) and the right ventricular outflow tract (RVOT) at basic cycle lengths of 600 and 400 ms.

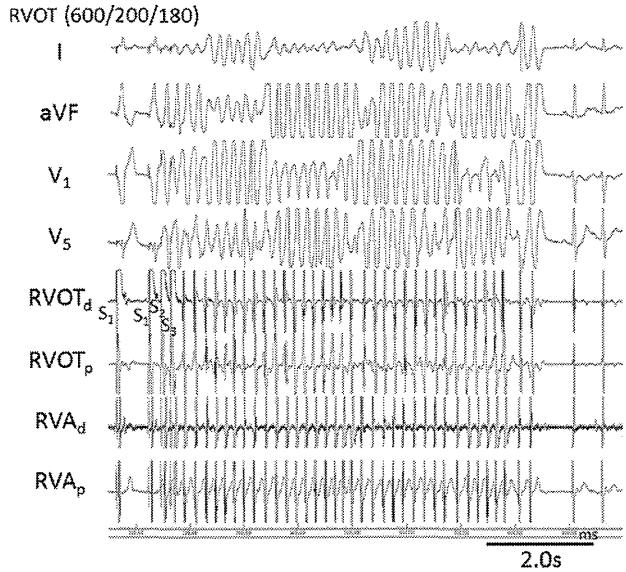

Fig. 2. Non-sustained polymorphic ventricular tachycardia was only induced during isoproterenol drip infusion in case 5. RVOT, right ventricular outflow tract; RVAd, the distal pair of the right ventricular apex; RVAp, the proximal pair of the right ventricular apex; RVOTd, the distal pair of the right ventricular outflow tract; RVOTp, the proximal pair of the right ventricular outflow tract.

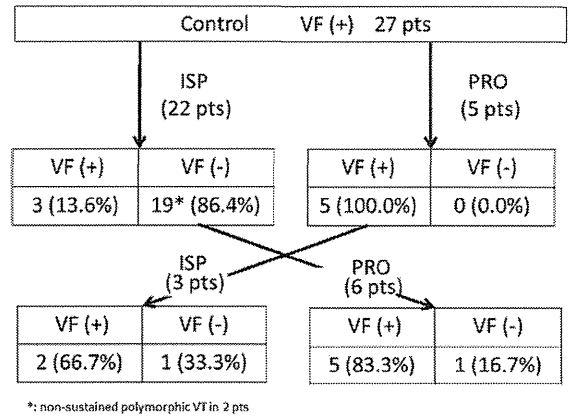

Fig. 3. Results of ventricular stimulation and pharmacological testing. VF(+): positive induction of ventricular fibrillation; VF(−), negative induction of ventricular fibrillation; ISP, isoproterenol; PRO, propranolol; pts, patients; VT, ventricular tachycardia.

6.14 ± 0.28 Hz in phases 1, 2, 3, 4, and 5, respectively. By contrast, DF_{ICE} in the control state was 5.63 ± 0.30 Hz, 5.75 ± 0.33 Hz, 6.00 ± 0.21 Hz, 6.15 ± 0.29 Hz, and 6.15 ± 0.38 Hz in phases 1, 2, 3, 4, and 5, respectively. DF_{ICE} during ISP was 5.94 ± 0.27 Hz, 6.11 ± 0.18 Hz, 6.20 ± 0.13 Hz, 6.18 ± 0.27 Hz, and 6.06 ± 0.29 Hz in phases 1, 2, 3, 4, and 5, respectively.

ISP significantly influenced the transition of DF_{ECG} and DF_{ICE} compared with the control state ($p = 0.0001$ in DF_{ECG}, $p = 0.005$ in DF_{ICE} by repeated-measure ANOVA; Fig. 6, upper panel). Note that DF_{ECG} and DF_{ICE} gradually increased from phase 1 to phase 3 but not from phase 3 to phase 5.

DF transition with phase after PRO

VF was induced in 10 patients after PRO. In the corresponding cases ($n = 10$), DF_{ECG} in the control state was 5.70 ± 0.38 Hz, 5.75 ± 0.59 Hz, 6.15 ± 0.36 Hz, 6.17 ± 0.56 Hz, and 6.20 ± 0.46 Hz in phases 1, 2, 3, 4, and 5, respectively. DF_{ECG} after PRO was 5.78 ± 0.45 Hz, 6.15 ± 0.40 Hz, 6.26 ± 0.47 Hz, 6.28 ± 0.43 Hz, and 6.49 ± 0.49 Hz in phases 1, 2, 3, 4, and 5, respectively. By contrast, DF_{ICE} in the control state was 5.72 ± 0.36 Hz, 5.81 ± 0.42 Hz, 6.11 ± 0.36 Hz, 6.20 ± 0.41 Hz, and 6.26 ± 0.49 Hz in phases 1, 2, 3, 4, and 5, respectively. DF_{ICE} after PRO was 5.93 ± 0.42 Hz, 6.20 ± 0.42 Hz, 6.29 ± 0.42 Hz, 6.36 ± 0.57 Hz, and 6.53 ± 0.55 Hz in phases 1, 2, 3, 4, and 5, respectively.

PRO significantly influenced the transition of DF_{ECG} and DF_{ICE} compared with the control state ($p < 0.0001$ in DF_{ECG}, $p < 0.0001$ in DF_{ICE} by repeated-measure ANOVA; Fig. 6, lower panel). Both DF_{ECG} and DF_{ICE} after PRO were relatively high in each phase of the control state.

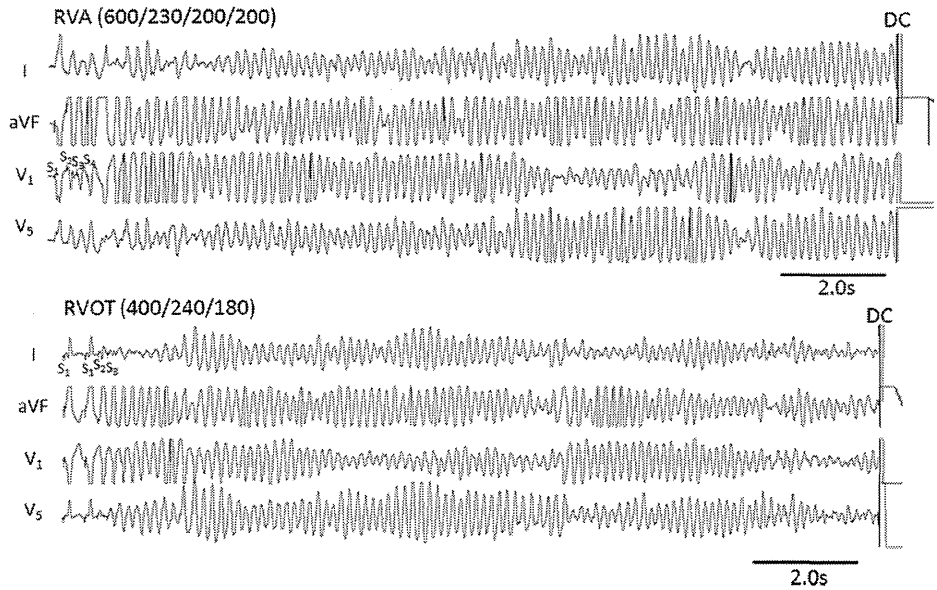

Fig. 4. Ventricular fibrillation was induced from triple mode ventricular stimulation ($S_1/S_2/S_3/S_4 = 600/230/200/200$ ms) at the right ventricular apex (RVA) in the control state (upper panel) and from double mode ventricular stimulation ($S_1/S_2/S_3 = 400/240/180$ ms) at the right ventricular outflow tract (RVOT) after propranolol i.v. (lower panel). Ventricular fibrillation was induced in a lower stimulation mode, and surface electrocardiogram was disorganized compared with that in the control state.

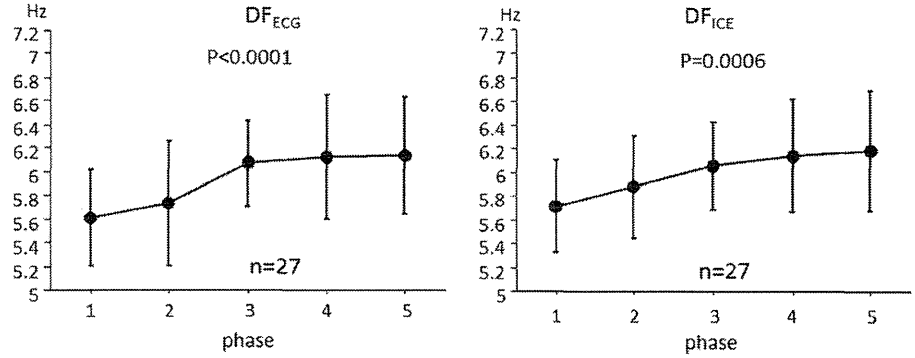

Fig. 5. Transition of dominant frequency of electrocardiogram (DF_{ECG}) and intracardiac electrogram (DF_{ICE}) in controls. DF_{ECG} and DF_{ICE} significantly increased with phase increase ($p < 0.0001$ and $p = 0.0006$, respectively).

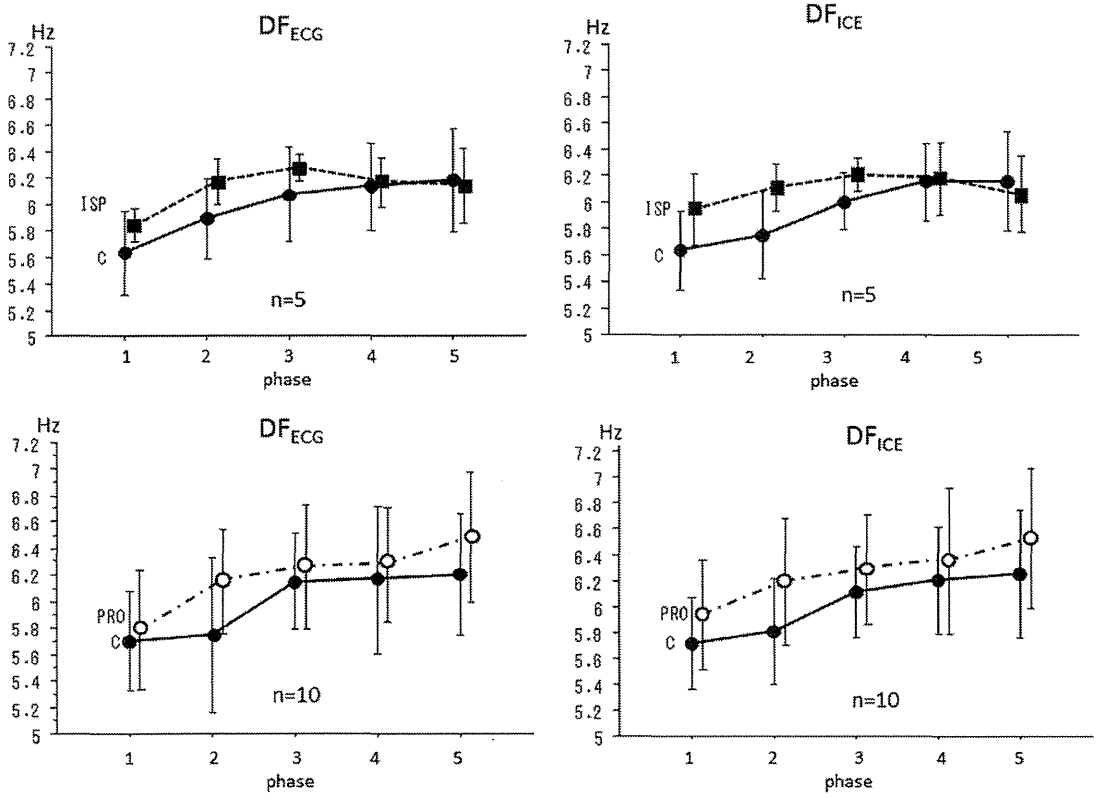

Fig. 6. Comparison of the transition of dominant frequency of electrocardiogram (DF_{ECG}) and intracardiac electrogram (DF_{ICE}) in the control state and drip infusion of ISP (upper panel) and PRO (lower panel). Transition of DF_{ECG} and DF_{ICE} with phase was significantly influenced by both ISP infusion ($p = 0.0001$ in DF_{ECG} and $p = 0.005$ in DF_{ICE}) and PRO ($p < 0.0001$ in DF_{ECG} and $p < 0.0001$ in DF_{ICE}). ISP suppressed the increase in DF with phase increase. Inversely, PRO increased DF in each phase compared with the control state. ISP, isoproterenolol; PRO, administration of propranolol.

Discussion

The occurrence of spontaneous VF in patients with BS is related to increases in vagal tone [3]. Inversely, VF electrical storm is sometimes prevented by the increase of sympathetic tone via ISP administration [7,20]. ST elevation in the right precordial leads, the specific ECG pattern of BS, increases by parasympathetic agonists and decreases by sympathetic agonists [3]. However, there is little information on the influence of adrenergic tone in the induction of VF by ventricular stimulation or VF frequency measurement by surface ECG and ventricular electrograms.

DF transition obtained by FFT during VF

In the present study, surface ECG was analyzed without signal processing because the shape of the waves is similar to that of sine waves. On the other hand, bipolar electrograms were analyzed after signal processing similar to the FFT analysis of atrial fibrillation as previously reported [13].

Electrical signal characteristics during VF in humans have been related to the mode of induction [21], duration of the arrhythmia [19], underlying heart disease [22], or drugs [10]. DF during VF has been reported as a potential physiologic indicator of VF duration [23].

DF_{ECG} and corresponding DF_{ICE} showed similar values and the change with phase in present study. The close relationship between DF_{ECG} and DF_{ICE} during the initial phase of induced VF (<3.3 min) has been reported [24]. Further, DF at the initial phase during induced VF was highly reproducible [25].

In the present study, both DF_{ICE} and DF_{ECG} significantly increased with phase. This is consistent with previous reports [10,11]. Initial phase DF was in the 8–12 Hz range in dogs and somewhat lower in humans [11]. In the present study, DF_{ICE} of phase 1 in patients with BS was 5.72 ± 0.38 Hz, which was higher than that in previous studies [8,10]. This suggests that the initial phase DF of induced VF in patients with BS may be higher than that in patients with apparent heart disease.

Influence of adrenergic activity on DF transition during VF

ISP has been reported to suppress arrhythmic storm in sporadic cases [7]. In the present study, DFs at the early phase 1 and 2 were relatively higher than those of control state. This can be explained by the ventricular ERP shortened by ISP. It seemed that the increase of DF at the late phase since phase 3 (4–8 s) was suppressed by ISP. On the other hand, PRO significantly accelerated DF from phase 1 compared with that in the control state.

In VF, a conduction delay occurs at the anterior wall and outflow tract of the right ventricle and is possibly exacerbated by an abrupt rise in vagal activity, inducing the random reentry that results in VF [3]. Therefore, VF suppression may result from the improvement of a conduction delay at the RVOT site by ISP. In another mechanism, beta-adrenergic stimulation induces the increased inward calcium current and attenuates excess of the outward current, resulting in action potential change, which suppresses phase 2 reentry [26]. Unfortunately, the detailed mechanism of VF suppression is not clear. However, the results of the present study are consistent with suppression of the electrical storm of VF by ISP [7,20] and a decrease of the J point in the right precordial lead [3].

Beta-blockers are ineffective for VF in patients with BS [3]. In the present study, beta-blockers have been shown to have the potential to aggravate VF in patients with BS.

Limitations of the present study

This study has several limitations. First, the sample sizes were small. Second, EPS during ISP after PRO may still be influenced by PRO because of the relatively long half-life of PRO. In fact, the increased rate of the heart rate of the negative VF group during EPS in ISP was significantly smaller than that of the positive VF group during EPS in ISP. This result may suggest the inducibility of VF during ISP depends on the effect of ISP on the sympathetic system. In other words, the inducibility of VF during ISP depends on the concentration of ISP. But, we need further examination of this issue. Third, 2 of the 5 patients underwent administration of PRO before ISP, and 5 of the 10 patients were subjected to ISP injection before PRO. The results of DF transition in two groups may be influenced by these pre-medications. Fourth, clinical and induced VF episodes in humans may have different spectral characteristics [9]. However, changes in DF from induced VF should be reflected by the substrate of VF and in the electrophysiological characteristics in patients with BS.

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Brugada症候群における下壁側壁誘導でのJ波の出現頻度と臨床的特徴

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【背景】下壁側壁誘導でのJ波を伴う特発性心室細動とBrugada症候群における心電図上の類似性・相違性が指摘されているが，詳細はいまだに不明である．今回，Naチャネル遮断薬負荷試験陽性例における薬物負荷前安静時心電図でのJ波の出現頻度について検討した．【対象と方法】対象は，Naチャネル遮断薬負荷試験にてtype 1 Brugada型心電図が確認された127例(平均年齢51±15歳，男性111例)である．既往の症状や不整脈から対象を4群〔Ⅰ群：非致死性不整脈(n=19)，Ⅱ群：失神(n=28)，Ⅲ群：無症状・Brugada型心電図(n=73)，Ⅳ群：致死性不整脈(n=7)〕に分類し，負荷前安静時心電図におけるJ波の出現頻度について検討した．【結果】J波は下壁側壁誘導で25例(19.7%)，下壁誘導のみで18例(14.2%)，側壁誘導のみで11例(8.7%)に出現し，下壁側壁誘導における各群のJ波の出現頻度には統計学的有意差があった〔Ⅰ群：4例(21.1%)，Ⅱ群：7例(25.0%)，Ⅲ群：9例(12.3%)，Ⅳ群：5例(71.4%)；$p<0.02$〕．何かしらの不整脈あるいは失神などの既往を有するⅠ・Ⅱ・Ⅳ群におけるJ波の出現頻度は，無症状のⅢ群に対して下壁誘導で有意差を認めた〔Ⅰ・Ⅱ・Ⅳ群 vs. Ⅲ群；13(24.1%) vs. 5(6.8%)；$p<0.02$〕が，側壁誘導では有意差を認めなかった．【結論】J波は致死性不整脈の既往を有するⅣ群において高頻度に合併し，また下壁誘導でのJ波は何かしらの不整脈発生基質の存在を反映している可能性が示唆された．

Keywords
- Brugada症候群
- J波
- 下壁側壁誘導

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Ⅰ．はじめに

心電図上のQRSからST部分にかけての軽微な異常，すなわちST上昇とQRS下降脚のノッチやスラーを形成するJ波は，病的意義の乏しい早期再分極所見として認識されている．そのうち，右側胸部誘導や下壁側壁誘導におけるST上昇とJ波は正

The Prevalence and Clinical Characteristics of J Wave in Patients with Brugada Syndrome
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常亜型とみなされている．Brugada症候群における心電図的特徴は右側胸部誘導におけるcoved型ST上昇であるが，同様のST異常を右側胸部誘導以外の下壁誘導などでも認めることがある．また，近年では特発性心室細動(IVF)において下壁側壁誘導でのJ波の合併が報告され，J波と突然死の関連が注目を集めている．Brugada症候群患者の下壁側壁誘導におけるJ波の特徴を明らかにするため，その出現頻度や部位などについて検討した．

Ⅱ．対象と方法

対象は，診断基準に準じた典型的type 1 Brugada型心電図がNaチャネル遮断薬負荷試験にて確認された127例(平均年齢51 ± 15歳，男性111例)である．なお，右側胸部誘導(V_1～V_3誘導)は，1肋間および2肋間高位の右側高位肋間誘導も合わせて全例記録した．Naチャネル遮断薬負荷試験は，既報のごとくピルジカイニドを用い，0.1 mg/kg/分を10分かけて投与した．症例は，臨床状より以下の4群とした[1),2)]．

Ⅰ群(19例)：非致死性不整脈(発作性心房細動，発作性上室頻拍，心房・心室期外収縮など)の既往例．

Ⅱ群(28例)：失神，前失神発作の既往例．

Ⅲ群(73例)：無症状．

Ⅳ群(7例)：致死性心室性不整脈の既往例(持続性心室頻拍，IVF)．

J波は，基線より1 mm (0.1 mV)上昇し下壁誘導(Ⅱ，Ⅲ，aV_F誘導)あるいは側壁誘導(Ⅰ，aV_L，V_4～V_6誘導)にてQRS終末部のノッチまたはスラーを認めるものとし，2誘導以上で認めた場合をJ波ありと定義した．以上の定義にしたがい，ベースライン(薬物負荷投与前)心電図におけるJ波の出現頻度，誘導数および誘導部位について検討した．

心室細動誘発試験：心室細動(VF)誘発試験は，右室心尖部および右室流出路から異なる基本周期(600，400 msec)か最短連結期180 msecでの2連発期外刺激，250 ppmまでの連続刺激，最短連結期200 msecまでにおける3連発期外刺激にて施行した．以上の刺激を行ったにもかかわらず誘発できなかった場合には，β遮断薬(プロプラノロール0.1 mg/kg)を投与して同様の刺激プロトコールで評価した．

表1　各グループにおけるtype 1 Brugada型心電図の出現頻度と心室細動誘発性

	Baseline		After NB		VF induction	
	Standard	+high leads	Standard	+high leads	Control	BB
Ⅰ群 n=19	17%	22%	67%	100%	73% n=11	73%
Ⅱ群 n=28	4%	27%	62%	100%	72% n=18	78%
Ⅲ群 n=73	17%	40%	65%	100%	67% n=15	87%
Ⅳ群 n=7	29%	57%	57%	100%	100% n=7	
Overall n=127	15%	36%	64%	100%	75% n=51	82%

NB：Naチャネル遮断薬，BB：β遮断薬

Ⅲ．結　　果

1．各群におけるtype 1 Brugada型心電図の出現頻度および心室細動誘発性

表1に各群におけるtype 1 Brugada型心電図の出現頻度，VF誘発性を示す．ベースライン(薬物負荷投与前)心電図においては，type 1 Brugada型心電図は通常誘導記録のみで平均15%，高位肋間誘導記録を含めると36%であった．Naチャネル遮断薬負荷下での通常誘導記録では64%であった．VF誘発試験は51症例で施行され，薬物非投与下では75%でVFの誘発が可能であった．薬物投与下においてはβ遮断薬を用いて誘発試験を行い，最終的には82%の症例でVFが誘発された．

2．下壁側壁誘導におけるJ波の出現頻度

J波は，下壁側壁誘導にて25例(19.7%)に認められた．各群のうちわけは，Ⅰ群4例(21.1%)，Ⅱ群7例(25.0%)，Ⅲ群9例(12.3%)，Ⅳ群5例(71.4%)であり，各群におけるJ波の出現頻度には有意差を認めた(図1)．このうち，18例(14.2%)は下壁誘導(Ⅱ，Ⅲ，aV_F誘導)に，11例(8.7%)は側壁誘導(Ⅰ，aV_L，V_4～V_6誘導)に限局して認められた．誘導部位別では各群に有意差は得られなかった(図2)．

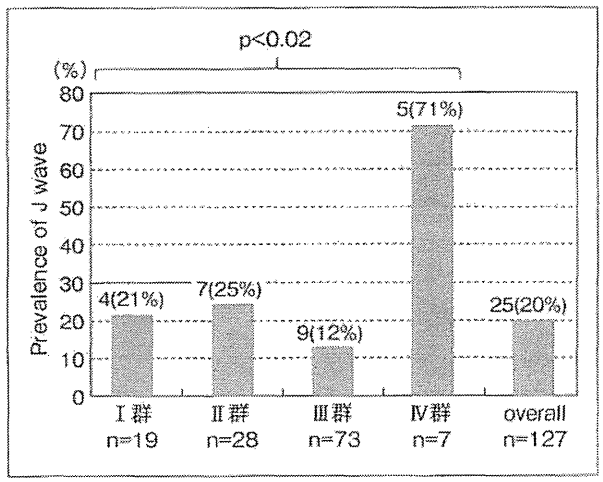

図1　各グループにおけるJ波の出現頻度

表2　各グループにおけるJ波の誘導数

	>7	6	5	4	3	2	1	Prevalence (≥1 lead)
Ⅰ群 n=19	0	0	0	0	4 (4)	0 (4)	2 (6)	32%
Ⅱ群 n=28	0	0	0	1	5 (6)	1 (7)	1 (8)	30%
Ⅲ群 n=73	0	0	1	1 (2)	5 (7)	2 (9)	12 (21)	29%
Ⅳ群 n=7	0	0	0	1	3 (4)	1 (5)	1 (6)	88%
Overall n=127	0	0	1 (1)	3 (4)	17 (21)	4 (25)	16 (41)	32%

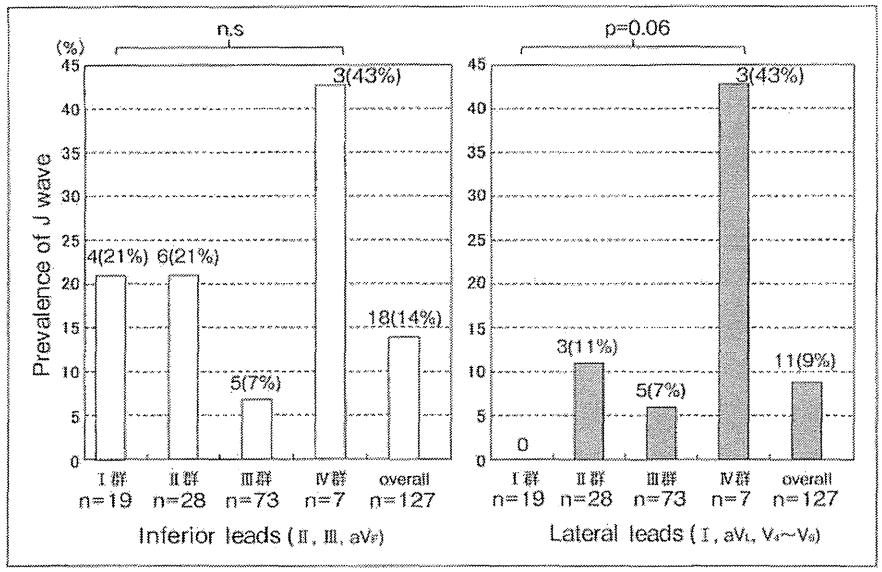

図2
下壁誘導(左)と側壁誘導(右)での各グループによるJ波の出現頻度

3. 各群におけるJ波の誘導数

各群におけるJ波を認めた誘導数を表2に示す．Ⅰ，Ⅱ，Ⅳ群では3つの誘導にJ波を認めることが最も多かったのに対して，Ⅲ群では定義上はJ波なしと判断するひとつの誘導のみにJ波を認める例が最も多かった．また，J波をひとつでも認めた誘導はⅠ，Ⅱ，Ⅲ群では30%前後にすぎなかったのに対して，Ⅳ群では8例中7例(87.5%)と，Ⅳ群におけるJ波の出現頻度は他の群に比して高い割合を示した．

4. 症状の有無別にみたJ波

何かしらの不整脈あるいは失神などの症状を有するⅠ群，Ⅱ群，Ⅳ群と症状を有さないⅢ群との間におけるJ波の出現頻度を比較検討した．下壁側壁誘導および下壁誘導においては，有症候例におけるJ波の出現頻度は無症候例と比較して有意に高かったが，側壁誘導におけるJ波の出現頻度には有意差を認めなかった(図3)．

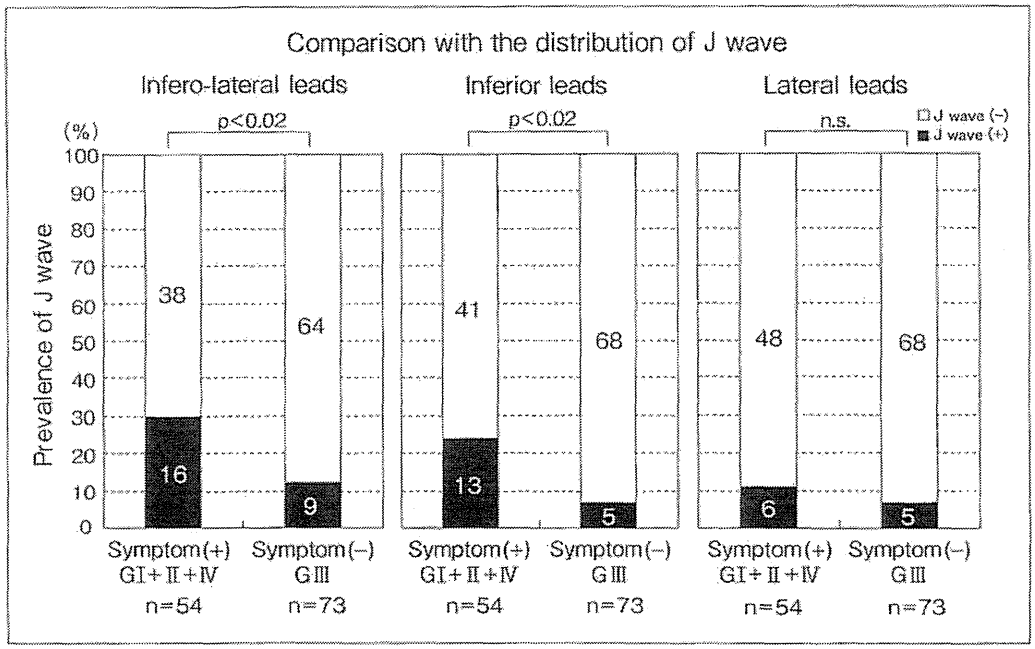

図3　症状の有無別でのJ波の頻度

左：下壁側壁誘導，中：下壁誘導，右：側壁誘導．

Ⅳ．考　　察

Naチャネル遮断薬(ピルジカイニド)負荷試験にて，type 1 Brugada型心電図が証明された127例の安静時心電図におけるJ波の出現頻度について検討した結果，以下の知見を得た．①下壁側壁誘導でのJ波の頻度は，致死性不整脈の既往のあるⅣ群(Brugada症候群)において他群よりも著明に高率であった．②J波の出現誘導数は，何かしらの症候を有するⅠ，Ⅱ，Ⅳ群では3つの誘導で認めることが多かったのに対し，Ⅲ群ではひとつの誘導のみに認めることが最も多かった．③何かしらの症状を有するⅠ，Ⅱ，Ⅳ群と症状を有さないⅢ群との比較では，J波は下壁側壁誘導と下壁誘導においてその出現頻度に有意差を認めたが，側壁誘導での有意差は認められなかった．

IVF例での下壁側壁誘導におけるJ波の合併がHaïssaguerreらによって報告され，従来良性所見と考えられてきたJ波(早期再分極)のなかに，病的なJ波が含まれることが明らかにされつつある[3]．Brugada症候群においてもしばしばJ波が下壁側壁誘導に合併することがあるが，Brugada症候群におけるJ波とIVFにおけるJ波との相違点については不明な点が多い．J波の出現頻度に関しては，HaïssaguerreらがIVF例での下壁側壁誘導において31％にみられたと報告したが，本研究における無症状を含めたBrugada型心電図例での頻度は約20％であった．しかし，VF既往例に限ると，少数例ではあるが当施設で高率(71％)に認められた．Letsasら[4]は，290例のBrugada症候群でのJ波(0.1 mV以上)の出現頻度は12％であり，このうち有症候88例では13例(15％)に認めるにすぎず，有症候例でのJ波を認めた症例と認めない症例において，不整脈イベントの発生を含み臨床的に相違はみられなかったと報告している．2009年にKamakuraら[5]が報告した330例におけるBrugada型心電図の長期予後によると，J波(早期再分極)は全体で10％に認められ，そのうちVF既往例では56例中10例(18％)に出現した．このKamakuraらの研究ではJ波の合併は不整脈イベント発生の予測因子であっ

た．以上のようにBrugada症候群におけるJ波は，既報では10～20%の出現頻度であり，J波自体の意義については統一見解を得ていないのが現状である．J波を認める心電図誘導部位と症状との関連については，Rossoら[6]はIVFと健常者・若年アスリートにみられるJ波との鑑別において，前胸部誘導(V_4～V_6誘導)での診断価値は低いと報告している．本研究においても無症候例では側壁誘導にJ波を認める例が多かったが，有症候例では下壁誘導において有意に多かったことから，IVFに限らず下壁誘導におけるJ波の存在は不整脈の存在を示唆する所見として注目すべきと思われた．

V．おわりに

本研究では，致死性不整脈既往例であるⅣ群でのJ波の合併頻度が，これまでの報告と比較しても高かったが，他群と比べて少数であるため，さらに症例を重ねて検討すべきと思われる．また，安静時心電図における典型的Brugad型type 1心電図は高位肋間誘導部位を含め36%と少なく，いわゆるBrugada signとJ波の出現との関係などについて検討していないため，これについても今後の検討課題である．

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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

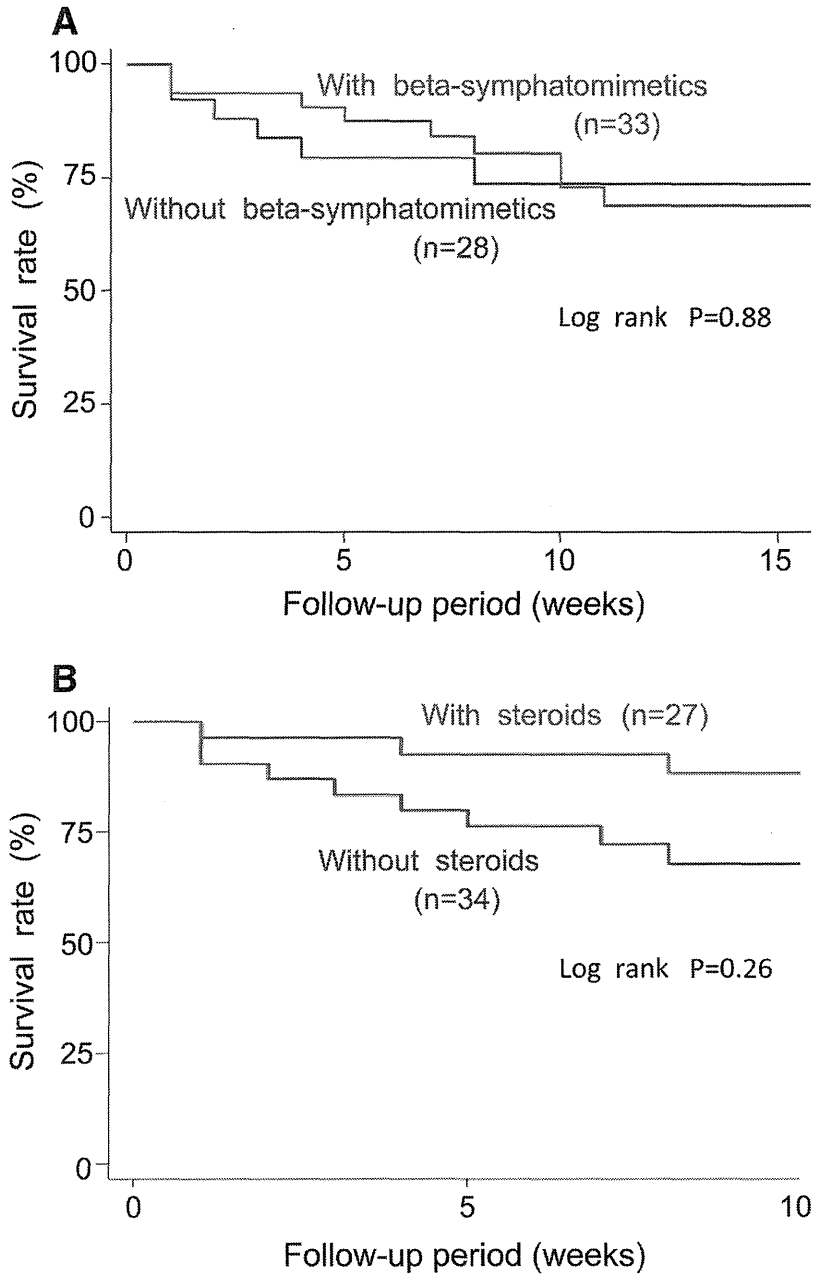

Figure. Kaplan-Meier survival curves (log-rank test and Cox proportional hazard model) for the primary endpoint (fetal death or neonatal death) in fetuses treated (**A**) with and without β-sympathomimetics and (**B**) with and without steroids. Follow-up period, time from diagnosis in utero to fetal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