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Risk Stratification for Asymptomatic Patients With Brugada Syndrome

—— Prediction of Induction of Ventricular Fibrillation by Noninvasive Methods ——

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Ventricular fibrillation (VF) is induced in some asymptomatic patients with Brugada syndrome (BS), but the prognostic value of programmed electrical stimulation (PES) in such patients is controversial. The clinical characteristics of 41 asymptomatic BS patients, divided into 2 groups according to whether VF was induced by PES (inducible VF group: n=13, non-inducible VF group: n=28) were evaluated. ST levels in the right precordial leads were measured before and after administration of pilsicainide and the abnormal late potential (LP) was evaluated on the signal-averaged electrogram. The ST level at V_2 at baseline in the inducible VF group was significantly higher than that in the non-inducible VF group ($p<0.05$). Pilsicainide induced significant ST segment elevation in both groups and the ST level after pilsicainide in the inducible VF group was higher than that in the non-inducible VF group ($p<0.01$). LP was more frequent in the inducible VF group than in the non-inducible VF group. The criterion of ST level >0.15 mV at baseline with pilsicainide-induced additional ST elevation >0.10 mV and positive LP showed high sensitivity (92%) and specificity (89%) for detection of PES-induced VF in asymptomatic BS patients. (*Circ J* 2003; **67:** 312–316)

Key Words: Brugada syndrome; Pilsicainide; Programmed electrical stimulation; Signal average electrogram; Ventricular fibrillation

Brugada syndrome (BS) is characterized by ST-segment elevation in leads $V_{1–3}$ with a right bundle branch block pattern and nocturnal sudden cardiac death caused by ventricular fibrillation (VF).[1,2] Patients with this syndrome who have experienced syncopal episodes or have been resuscitated from cardiac arrest have a poor prognosis if they do not receive an implantable cardioverter defibrillator (ICD). Although the prevalence of Brugada-type ECG change in healthy subjects is approximately 0.1–1%, their prognosis of is relatively good compared with symptomatic patients.[3–10] However, some asymptomatic patients become symptomatic and sudden cardiac death can occur with the first VF attack, so it is a problem in Japan of how to treat asymptomatic patients with a typical Brugada-type ECG who are detected by daily medical check-up. The results of some recent studies regarding the prognostic value of programmed electrical stimulation (PES) for patients with BS are conflicting;[6–9] Priori et al reported that the factors that predicted cardiac events were spontaneous ST elevation in leads $V_{1–3}$ and episodes of syncope, but that VF inducible by PES did not indicate an increased risk of cardiac arrest,[7] whereas Brugada et al reported that inducibility of ventricular arrhythmia and an abnormal ECG without provocation were predictors of arrhythmic events.[8,9] However, an electrophysiological study (EPS) is expensive and invasive, and sometimes results in complications, so it should not be carried out for all asymptomatic patients who show a Brugada-type ECG, but only for those patients for whom there is a high risk for a cardiac event. Because it is currently impossible to accurately predict the occurrence of cardiac events in asymptomatic patients, the present study was designed to determine noninvasive methods that could predict induction of VF by PES in asymptomatic patients with Brugada syndrome. For this purpose, the clinical characteristics of asymptomatic patients in whom VF was induced by PES were assessed, and the differences between the clinical values in asymptomatic patients with PES-induced VF and those without PES-induced VF were studied using noninvasive methods (a sodium channel blocker [pilsicainide] challenge test and a signal averaged electrogram).

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Methods

Patients

The subjects of this study were 41 male asymptomatic patients with BS (age 27–66 years; mean age, 45±10 years). A Brugada-type ECG was defined as late r' wave (>0.2 mV) and ST segment elevation (>0.1 mV).[3] All of the subjects

Table 1 Electrophysiological Characteristics of the Syudy Patients

	All (n=41)	*Inducible VF (n=13)*	*Non-inducible VF (n=28)*	*p value**
ST level (mV)				
V_1 at rest	*0.13±0.06*	*0.13±0.06*	*0.13±0.06*	*0.747*
V_1 after pilsicainide	*0.25±0.16*	*0.27±0.15*	*0.24±0.16*	*0.538*
Δ ST at V_1	*0.12±0.12*	*0.13±0.10*	*0.11±0.13*	*0.320*
V_2 at rest	*0.27±0.12*	*0.35±0.16*	*0.24±0.08*	*0.017*
V_2 after pilsicainide	*0.60±0.33*	*0.81±0.32*	*0.50±0.29*	*0.008*
Δ ST at V_2	*0.33±0.26*	*0.46±0.21*	*0.26±0.25*	*0.008*
Signal average electrogram				
f-QRS (ms)	*116.3±9.2*	*120.6±9.0*	*114.3±8.8*	*0.032*
LAS40 (ms)	*40.8±9.1*	*46.9±8.4*	*38.0±8.1*	*0.007*
RMS40 (μV)	*17.6±8.4*	*12.2±4.4*	*20.1±8.6*	*0.001*

Data are presented as the mean value±SD.
**p value for difference between asymptomatic patients with inducible VF and non-inducible VF.*
Δ ST, the difference betweeen ST level before and after administration of pilsicainide; f-QRS, filtered QRS; LAS40, duration of low amplitude signal <40 μV in the terminal filterd QRS; RMS40, root mean square voltage of the terminal 40 ms in the filterd QRS; VF, ventricular fibrillation.

had right bundle branch block with spontaneous ST elevation without drug provocation. Two patients had a family history of unexplained sudden death at less than 50 years of age, but there was no obvious family history of BS. Echocardiography, right ventriculography and cardiac biopsy from the inter-ventricular septum of the right ventricle were performed in all patients but no abnormalities were found.

Classification of the Patients

The patients were divided into 2 groups based on the results of the EPS: one group in which VF was induced by PES (inducible VF group, n=13) and one group in which VF was not induced by PES (non-inducible VF group, n=28).

Pharmacological Challenge With a Sodium Channel Blocker

Pilsicainide was administered to all patients (150 mg po in 14 patients; 1 mg/kg iv over a 6-min period in 27 patients) and the ST level was measured at the J point in leads V_1 and V_2, before and after administration of pilsicainide, to calculate the difference in the ST level (ΔST). The occurrence of ventricular arrhythmia after administration of pilsicainide was also evaluated.

Signal Averaged Electrogram

The presence of an abnormal late potential (LP) was investigated using a signal-averaged electrogram (SAECG: ART 1200EPX, noise level <0.3 μV, high-pass filtering of 40 Hz using a bi-directional four-pole Butterworth). The filtered QRS duration, the root mean square voltage of the terminal 40 ms in the filtered QRS complex (RMS40), and the duration of low-amplitude signals (<40 μV) in the terminal filtered QRS complex (LAS40) were measured using the SAECG. The LP was considered to be positive when 2 criteria were met (RMS40 <20 μV and LAS40 >38 ms).

Electrophysiological Study

After obtaining written informed consent, an EPS was performed in all 41 patients with BS. All antiarrhythmic drugs were discontinued for at least 5 drug half-lives beforehand. PES was performed at an intensity twice the threshold for 2 ms through the distal electrodes placed at the right ventricular apex (RVA), the right ventricular outflow tract (RVOT) and the left ventricle (LV), using a

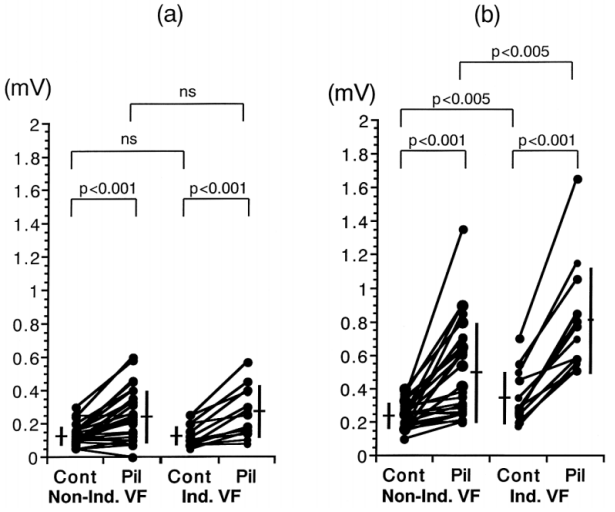

Fig 1. Right precordial ST levels before and after administration of the sodium channel blocker in asymptomatic patients with Brugada syndrome. (a) Changes in the ST level in lead V_1 in asymptomatic patients in whom VF was not induced by PES (Left panel) and in those in whom VF was induced by PES (Right panel). Administration of pilsicainide resulted in augmentation of the ST level in both groups. (b) Changes in the ST level in lead V_2 in asymptomatic patients in whom VF was not induced by PES (Left panel) and in those in whom VF was induced by PES (Right panel). Administration of pilsicainide resulted in marked augmentation of the ST level in both groups. Con., before administration of pilsicainide; Pil, after administration of pilsicainide; Non-ind VF, asymptomatic patients without induced VF by PES; Ind VF, asymptomatic patients with induced VF by PES. NS, not significant.

SEC3105 Nihon-Koden pulse generator. The protocol included an 8-beat ventricular paced drive train at 2 basic cycle lengths (600 and 400 ms) followed by a decremental introduction of up to triple extrastimuli and 5-beat rapid burst pacing up to 270 beats/min. The coupling interval of extrastimuli was not less than 180 ms. The end-point was either induction of VF or completion of the protocol. VF was defined as an ECG consisting of chaotic deflections of varying amplitude and counter.

Statistical Analysis

Quantitative values are expressed as means±1SD. Statis-

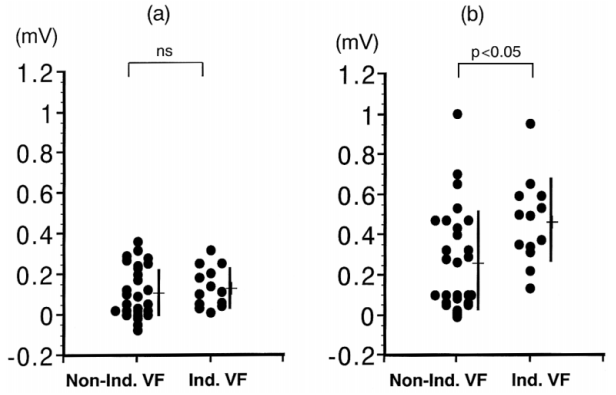

Fig 2. Augmentation of ST level by administration of pilsicainide. (a) The difference in the ST level in lead V_1 before and after administration of pilsicainide (ΔST). There was no difference between the induced VF and that of non-induced VF groups. (b) The difference in the ST level in lead V_2 before and after administration of pilsicainide. ΔST of the induced VF group was larger than that of the non-induced VF group.

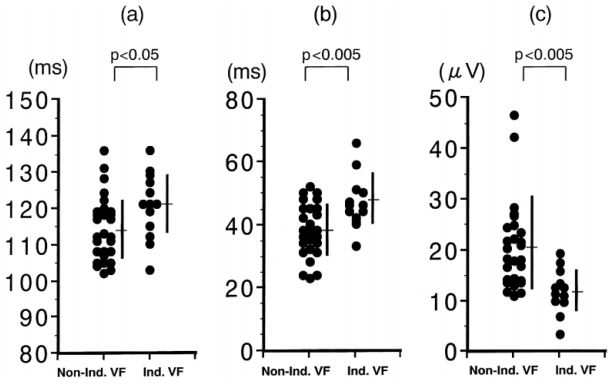

Fig 3. Signal average electrogram and late potential (a) Total QRS duration. There was no difference between the total QRS duration in the patients in whom VF was induced by PES and those in whom VF was not induced by PES. (b) LAS40 was significantly increased in asymptomatic patients with induced VF by PES. (c) RMS 40 was significantly decreased in asymptomatic patients with induced VF by PES.

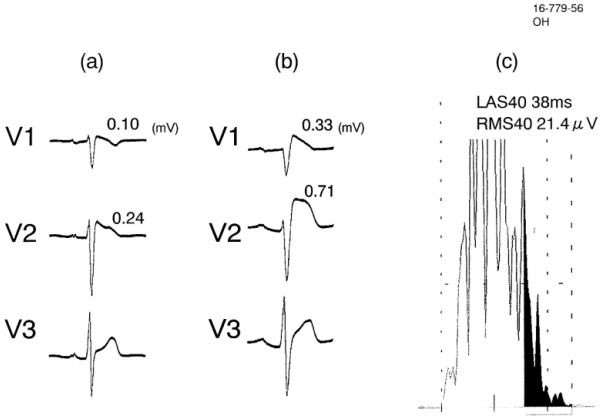

Fig 4. Effects of administration of pilsicainide and late potential in an asymptomatic patient without induced ventricular fibrillation by PES. Although VF was not induced by PES, the ECG showed the typical coved-type ST elevation (a) and the ST elevation was augmented by administration of pilsicainide (b). In this case, late potential was negative (c).

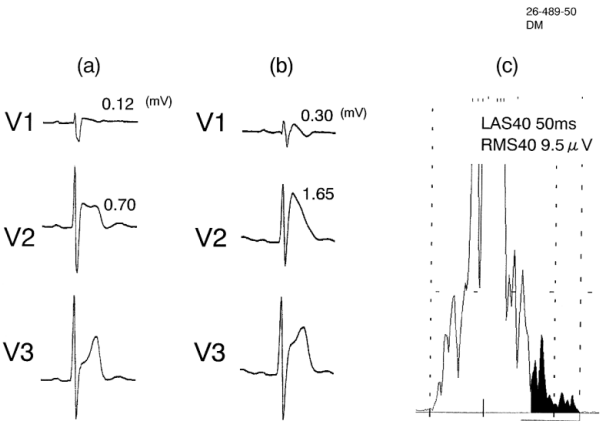

Fig 5. Effects of administration of pilsicainide and late potential in an asymptomatic patient with induced ventricular fibrillation by PES. The ECG showed the typical coved type ST elevation (a) that was augmented by administration of pilsicainide (b). In this case, late potential was positive (c).

tical significance of differences was analyzed by the Mann-Whitney U-test for unpaired values. A value of $p<0.05$ was considered statistically significant.

Results

Clinical Characteristics in Asymptomatic Patient With BS

The ST levels at leads V_1 and V_2 were augmented after administration of pilsicainide (Table 1). A ventricular arrhythmia occurred spontaneously in 4 (9.8%) of the asymptomatic patients after administration of pilsicainide: premature ventricular contractions in 3 patients and polymorphic ventricular tachycardia in 1 patient. The SAECG often showed abnormal values. During the EPS, VF was induced in 13 (31.8 %) of the patients, but not in 28 (68.3%).

Differences Between the Clinical Characteristics of the Inducible VF and Non-Inducible VF Groups

The ST levels in the right precordial leads were augmented after administration of pilsicainide in both groups, and there were no differences in the ST level in lead V_1 between the groups (Table 1, Fig 1a). The voltage of the ST level in lead V_2 was significantly high at rest and was augmented after administration of pilsicainide in the inducible VF group compared with the non-inducible VF group (Fig 1b). There was no difference between the ΔST of V_1 in either group, but ΔST of V_2 was significantly augmented in the inducible VF group (Fig 2). Ventricular arrhythmia occurred after administration of pilsicainide in 3 patients in the inducible VF group and in 1 patient in the non-inducible VF group, and the SAECG showed abnormal values more frequently in the inducible VF group than in the in non-inducible VF group (Figs 3–5).

The ST level at rest, the ΔST with pilsicainide challenge and the LP all showed high sensitivity, but low specificity for detection of induction of VF by PES in the asymptomatic patients individually. The sensitivity and specificity of the ST level in V_2 >0.15 mV at baseline were 100% and 21%, respectively, of ΔST at rest >0.1 mV in V_2 with administration of pilsicainide were 100% and 54%, respectively, and of the positive late potential of RMS40 >38 μV and LAS40 <20 ms were 92% and 64%, respectively. A

combination of all these values showed high sensitivity (92%) and specificity (89%) for detection of induction of VF by PES in asymptomatic patients.

Follow-up

The mean follow-up period for the patients was 28±24 months (range, 1–77 months). There was no difference between the follow-up periods for patients in the inducible VF group (average 18±16 months; range, 1–65 months) and those in the non-inducible VF group (average 33±26 months; range, 1–77 months, p=0.076). New cardiac events (ie, syncope, sudden death or documented VF) did not occur in any of the patients.

Discussion

In 1992 Brugada et al reported patients who had VF with a right bundle branch morphology and ST-segment elevation at rest[1] and it has since been reported that the VF can be induced by PES in most symptomatic patients with BS and in approximately 30% of asymptomatic patients, although the results regarding the prognostic value of inducing VF are conflicting[6–10] Although the prevalence of Brugada-type ECG change is approximately 0.1–1% in healthy subjects, their prognosis has been reported as relatively good compared with symptomatic patients[3–8] except for one early study[11] However, some asymptomatic patients become symptomatic and in some patients sudden cardiac death can occur with the first VF attack. Therefore, a clinical examination that enables high-risk asymptomatic patients to be differentiated from those at low risk asymptomatic patients is essential. Some ECG markers have been suggested as the criterion of high-risk patients[12,13] Priori et al reported that spontaneous ST-segment elevation and a history of syncope predict high-risk patients, but PES failed to predict the spontaneous occurrence of VF[7] Moreover, in symptomatic patients who had an unexplained syncope attack or had been resuscitated from cardiac arrest, induction of VF by PES did not predict the recurrence of a cardiac event[14] Brugada et al reported that inducibility of ventricular arrhythmia and spontaneous ST elevation were predictors of the spontaneous occurrence of an arrhythmia[8,9,11] and they also showed the effectiveness of PES for predicting arrhythmic events in asymptomatic patients. Both of the above studies showed that symptomatic patients with a typical Brugada-type ECG who did not received an ICD had a poor prognosis, but their results regarding the effectiveness of PES for predicting cardiac events in asymptomatic patients with a typical Brugada-type ECG were contradictory. Priori et al recommended that larger numbers of patients needed to be studied using the same protocol and with longer follow-up periods before conclusive statements can be made on the prognostic value of PES in patients with BS[7]

ST Elevation and Administration of a Sodium Channel Blocker

The ST elevation in patients with BS has been explained by abnormal shortening of the epicardial action potential duration and phase 2 reentry at the right ventricle[15–17] A sodium channel blocker unmasks or augments ST elevation[18] because a decrease in the sodium current induces a prominent transient outward current, which results in marked shortening of the epicardial action potential duration[16] The results of the present study showed that ST levels in the right precordial leads were augmented by administration of pilsicainide in asymptomatic patients, particularly those with inducible VF, and we consider that the response of epicardial repolarization to a sodium channel blocker is more sensitive and augmented in the asymptomatic patients with PES-induced VF.

Ventricular Arrhythmia and Sodium Channel Blocker

Administration of pilsicainide induced ventricular arrhythmia in 4 patients, one of whom developed polymorphic ventricular tachycardia. The induction of ventricular arrhythmia by administration of pilsicainide was not associated with ST level and LP, and occurred frequently in the inducible VF group. It is thought that asymptomatic patients with pilsicainide-induced ventricular arrhythmia are at high risk for the development of cardiac events, but long-term follow-up is needed to confirm this finding.

Late Potential and Conduction Abnormality

Although ST elevation has been explained by a repolarization abnormality, the conduction abnormality in patients with BS has been demonstrated clinically. Late activation in the right ventricle has been demonstrated by body surface mapping[19] and SAE has shown abnormal LP[20–23] A morphological abnormality in the right ventricle also has been shown[24] and recently, Nagase et al reported that an epicardial conduction abnormality exists in patients with BS[25] Moreover, we have reported that a conduction abnormality exists not only in the ventricular myocardium, but also in the atrial myocardium[26] The present study showed that abnormal LP was frequent in asymptomatic patients, especially in those with PES-induced VF, indicating that a conduction abnormality is an underlying factor in asymptomatic patients with BS in whom VF can be induced by PES. This finding is similar to the results of a recent study in which electrophysiologic characteristics were studied in symptomatic patients with BS[14] and our results indicate that repolarization and depolarization abnormalities play an important role in the induction of VF by PES and in the spontaneous occurrence of ventricular arrhythmia.

Sensitivity and Specificity for Detection of PES-Induced Ventricular Fibrillation

The ST level at rest, the augmentation of the ST level by pilsicainide and the LP were evaluated in the asymptomatic patients with BS and we found that these indices were more abnormal in the asymptomatic patients with PES-induced VF. The sensitivity of these indices for detection of PES-induced VF was high, but the specificity of each of these indices was quite low. A combination of these indices had high sensitivity and improved specificity for detection of induction of VF by PES. Although it is not clear whether these combined indices are useful for predicting the prognosis of patients with BS, an EPS could be omitted if these indices was positive in asymptomatic patients with BS.

Study Limitations

We were not able to detect genetic abnormalities, and the response to sodium channel blockade and occurrence of abnormal LP could depend on BS genotype. However, determining the genotype in BS is relatively difficult because the prevalence of mutations in the cardiac sodium channel is reportedly only 15%[6] The ST levels in the right precordial leads can vary in patients with BS[28] and that an abnormal ECG can sometimes become normal. Although we conclude from the present results that a useful criterion of

ST elevation is >0.15 mV in lead V_2, some patients with a normalized ECG would not be detected by this criterion. Thus if a patient was susceptible for BS, the ECG recording should be repeated. Another limitation of this study is the relatively small number of patients and short follow-up periods, because this study was performed in one institute. Cardiac events did not occur in any of the asymptomatic patients, but further study is needed to determine the long-term prognosis of asymptomatic patients with BS.

We used intravenous and oral administration of pilsicainide, but we did not compare the serum drug concentration with the 2 administration methods and it is possible that the ST level and occurrence of ventricular arrhythmia after administration of pilsicainide might be influence by the route of administration.

Conclusions

Asymptomatic BS patients with induced ventricular fibrillation by PES have an abnormal repolarization response to administration of a sodium channel blocker and a conduction abnormality. The criterion of ST level (V_2) at rest of >0.15 mV, augmentation of ST level (V_2) after administration of pilsicainide of >0.1 mV, and positive LP (RMS40 >38 μV and LAS40 <20 ms) have high specificity and sensitivity for detection of PES-induced VF in asymptomatic patients with BS.

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