Relationship Between ST-Segment Morphology and Conduction Disturbances Detected by Signal-Averaged Electrocardiography in Brugada Syndrome

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Background: Although arrhythmogenesis of Brugada syndrome is still unknown, it has been reported to be associated with conduction disturbances. Two ST-segment morphologies (coved and saddle-back patterns) have been described in this syndrome. No study has sought to determine which morphology has stronger conduction disturbances, thereby associating with life-threatening events.

Methods: Forty-six patients who presented the Brugada-type ECG with either of a characteristic coved ($n = 25$) or saddle-back ($n = 21$) pattern of ST-segment morphology underwent signal-averaged ECG (SAECG). SAECG parameters, and the history of life-threatening events defined as syncope or aborted sudden death, were compared between groups.

Results: Although filtered QRS duration did not differ between groups, the incidence of late potentials in the coved group was higher than in the saddle-back group (22 patients (88%) versus 4 patients (19%); $P < 0.01$), showing lower RMS_{40} and longer LAS_{40} . Life-threatening events occurred in 17 patients (68%) in the coved group and 7 patients (33%) in the saddle-back group ($P = 0.02$).

Conclusion: The coved pattern of ST segment was more closely related to conduction disturbances than the saddle-back pattern in patients with Brugada-type ECG. Life-threatening events were more common in patients with the coved ST-segment elevation. Conduction disturbances in the coved pattern of ST segment may reflect a substrate of arrhythmogenesis in Brugada syndrome.

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Brugada syndrome; ST segment; conduction disturbances; signal-averaged ECG

The Brugada syndrome, which is characterized by a pattern of right bundle branch block (RBBB) and ST-segment elevation in electrocardiogram (ECG) leads V_1 through V_3 (Brugada-type ECG) is considered a primary electrical disease of the heart.^{1–6} The precise pathophysiology for the arrhythmogenesis in this syndrome has yet to be worked out fully. However, recent experimental studies have supported the hypothesis that the malignant ventricular arrhythmias that occur in this syndrome are caused by repolarization abnormalities.^{2,5,6}

An alternative explanation of arrhythmogenesis in this syndrome is delayed conduction occurring in the right ventricle,^{7–10} which is consistent with the conduction abnormality hypothesis. We recently reported that late potentials (LP) detected by signal-averaged ECG (SAECG) are a noninvasive risk stratifier in patients with Brugada syndrome.¹¹ This observation supports the conduction abnormality hypothesis.

On the other hand, two morphologies of ST-segment elevation (coved and saddle-back) have

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been described in patients with Brugada syndrome.^{8,12-14} Previous studies have suggested that the coved ST-segment elevation is associated with greater arrhythmogenic potential,¹²⁻¹⁴ but this relationship has not been well established. The purpose of the present study was to determine whether the coved pattern of ST-segment elevation is in fact more closely associated with conduction disturbances and life-threatening events than the saddle-back pattern of ST-segment elevation in patients with the Brugada-type ECG, and to gain insight into the arrhythmogenic nature of the electropathology.

METHODS

Patient Population

Sixty consecutive patients referred to Toho University Ohashi Hospital between December 1996 and August 2001 who presented an ECG with either

persistent or transient RBBB pattern with marked ST-segment elevation (≥ 0.1 mV, either coved or saddle-back pattern) in leads V_1 , V_2 , or V_3 during sinus rhythm were enrolled (Fig. 1). Although all patients underwent SAECG, eight patients were excluded from data analysis because they lacked characteristic ECG features (an RBBB pattern with marked ST-segment elevation in the right chest leads) at the time they underwent SAECG. Six patients with the typical widened S-wave and wide QRS complex (≥ 120 ms) in the left lateral leads were also excluded from data analysis. Therefore, data from 46 patients (48 ± 15 years, 42 men) were available for analysis. These patients were divided into two groups based on the morphology of ST-segment elevation by the resting ECG recorded at the SAECG: coved or saddle-back. When a patient presented both morphologies in leads V_1 to V_3 (e.g., "coved" in V_1 , "saddle-back" in V_2 and V_3), the patient was placed in the coved

Figure 1. (A) Twelve-lead ECG during sinus rhythm showing a Brugada-type ECG classified as coved group. (B) Twelve-lead ECG during sinus rhythm showing a Brugada-type ECG classified as saddle-back group.

group. The patients placed in the saddle-back group presented only "saddle-back" in leads V_1 to V_3 . Because both patterns of ST-segment elevation may occur in the same patients, the patients were classified by the pattern at SAECG. Cardiac abnormalities were ruled out using imaging techniques, cardiac catheterization, and endocardial biopsy. No patient had used antiarrhythmic drugs or had an electrolyte disturbance at the time the characteristic ECG findings were identified. A patient was considered to have a life-threatening event if he or she had a history of recurrent syncope attacks of unknown etiology or aborted sudden death while undergoing SAECG.

Thirty normal individuals who were matched for age and gender also underwent SAECG as the control.

Measurement of ST-Segment Elevation

The magnitude (mV) of ST-segment elevation in the right chest leads was automatically measured using the CH2000 System (Cambridge Heart, Inc., Bedford, MA, USA) 80 ms after the J point.¹⁵ The maximum ST-segment elevation in the right chest leads was determined in each patient.

Measurement of SAECG

Conduction disturbances were analyzed using the SAECG system (1200 EPX, Arrhythmia Research Technology, Inc., Austin, TX, USA). This analysis is based on the quantitative time-domain measurements of the filtered vector magnitude of the orthogonal Frank X, Y, and Z leads. The QRS complexes (beats ≥ 200) were amplified, dig-

itized, averaged, and filtered with a high-pass filter (40 Hz). Three parameters were assessed via a computer algorithm: (1) the filtered QRS duration (f-QRS); (2) the root-mean-square voltage of the terminal 40 ms in the f-QRS complex (RMS_{40}); and (3) the duration of low amplitude signals $<40 \mu V$ in the terminal f-QRS complex (LAS_{40}). In the present study, LP were considered positive when two criteria ($RMS_{40} < 20 \mu V$ and $LAS_{40} > 38$ ms) were met.¹¹

Statistical Analysis

Data are expressed as the mean $\pm$ SD. Inter-group differences in each SAECG parameter were assessed by one-way analysis of variance, applying the post-hoc Scheffe's F test. The maximum magnitude of ST-segment elevation between two groups was assessed by the unpaired chi-squared test. Frequency comparisons were made by the Fisher's exact test or the contingency t test. The relationship between the coved pattern of ST elevation and the life-threatening event was also evaluated using the chi-squared test, calculating the odds ratio and 95% confidence interval (CI). A value of $P < 0.05$ was considered statistically significant.

RESULTS

Signal-Averaged ECG Results

Twenty-five patients (49 ± 13 years, 23 men) were classified into the coved group, and the remaining 21 patients (46 ± 17 years, 19 men) were classified into the saddle-back group. The SAECG results are shown in Table 1. A characteristic

Table 1. Results of Signal-Averaged Electrocardiography and Magnitude of ST-Segment Elevation

	Control Group (n = 30)	Coved Group (n = 25)	Saddle-Back Group (n = 21)	P Value ^a
Determinate LP	2 (7%)	22 (88%) ^{b,c}	4 (19%)	
f-QRS (ms)	97.7 ± 10.3	117.0 ± 12.5^c	110.0 ± 10.2^c	<0.01
$RMS_{40} \mu V$	44.6 ± 21.3	$13.4 \pm 6.8^{b,c}$	27.7 ± 12.0^c	<0.01
LAS_{40} (ms)	28.7 ± 6.9	$45.7 \pm 9.7^{b,c}$	30.9 ± 7.0	<0.01
Mean maximum ST elevation (mv)		0.27 ± 0.09	0.27 ± 0.10	

^a P Value for the analysis of variance for comparison among groups; ^b $P < 0.01$ compared to saddle-back group; ^c $P < 0.01$ compared to control group.

f-QRS = filtered QRS duration; RMS_{40} = the root-mean-square voltage of the terminal 40 ms in the filtered QRS; LAS_{40} = the duration of low-amplitude signals $<40 \mu V$ in the terminal filtered QRS; and LP = late potentials.

Figure 2. (A) Electrocardiographic tracings in leads V_1 to V_3 and the SAECG for the same patient as shown in Figure 1A. The f-QRS is 114 ms. The late potentials, represented by the shaded area, are positive, showing an RMS_{40} of 14.8 μV , and an LAS_{40} of 43 ms. (B) Electrocardiographic tracings in leads V_1 to V_3 and the SAECG for the same patient as shown in Figure 1B. The f-QRS is 92 ms. The late potentials, represented by the shaded area, are negative, showing an RMS_{40} of 25.2 μV , and an LAS_{40} of 34 ms.

Brugada-type ECG was observed at the time of SAECG in all patients (Fig. 2). Although the f-QRS was similar in the coved group and the saddle-back group, the RMS_{40} was lower in the coved group than in the saddle-back group ($P < 0.01$), whereas the LAS_{40} was greater in the coved group than in the saddle-back group ($P < 0.01$). Twenty-two (88%) patients in the coved group and four (19%) patients in the saddle-back group had determinate LP. The incidence of determinate LP was higher in the coved group than in the saddle-back group ($P < 0.01$). In the control group, two (7%) of the 30 patients had determinate LP. Comparing the control group to the saddle-back group, the f-QRS was greater and the RMS_{40} was lower in the saddle-back group ($P < 0.01$, respectively); whereas the LAS_{40} and the incidence of determinate LP were similar ($P = 0.26$ and $P = 0.21$, respectively). On the other hand, all SAECG parameters in the coved group, including

the incidence of determinate LP, indicated greater conduction disturbances than in the control group ($P < 0.01$, respectively).

The mean maximum magnitude of ST-segment elevation in the right chest leads was similar in the coved group and the saddle-back group ($P = 0.95$) (Table 1).

ST-Segment Morphology and Life-Threatening Events

Comparison of clinical variables between two patient groups is shown in Table 2. There were no differences between the two patient groups in their clinical variables such as age, gender, and familial history. Twenty-four patients had a history of life-threatening events defined as syncope (15 patients) and aborted sudden death (nine patients). In 12 of these patients, ventricular

Table 2. Comparison of Clinical Variables Between Patients with Coved and Saddle-Back ST-Segment Elevation

	Coved Group (n = 25)	Saddle-Back Group (n = 21)	P Value	Odds Ratio	(95% CI)
Age (mean $\pm$ SD)(yrs)	49 $\pm$ 13	46 $\pm$ 17	0.49		
Gender, male	23	19	0.62		
Familial history of sudden death	11	4	0.12		
Life-threatening event	17 (68%)	7 (33%)	0.02	4.3	(1.2, 14.6)
Syncope	9	6			
Aborted sudden death	8	1			

CI = confidence interval.

fibrillation (VF) had been documented before entry into the study. Fifteen patients had a history of one or more family members who suffered sudden death of unknown etiology. The frequency of life-threatening events was higher in the coved group than in the saddle-back group ($P = 0.02$).

DISCUSSION

At present, the role of conduction disturbance in the right ventricle in arrhythmogenesis of the Brugada syndrome has not been established, but the high incidence of LP detected by SAECG in Brugada syndrome is well known. On the other hand, recent studies have been described as an association between the coved ST-segment elevation and cardiac events in this syndrome. However, no study has reported a relationship between the morphology of ST segment (coved and saddle-back patterns) and conduction disturbances so far.

ST-Segment Morphology and Conduction Disturbances

The present study showed that the patients in the coved group had more extensive conduction disturbances than those in the saddle-back and control groups. In addition to this finding, the maximum ST-segment elevation was similar in the both patient groups. These observations support the hypothesis that the coved ST-segment elevation indicates the existence of greater conduction disturbances than the saddle-back ST-segment elevation regardless of the magnitude of the ST-segment elevation.

As compared with saddle-back group to control group, although the LAS_{40} and the incidence of determinate LP were similar, the f-QRS and the

RMS_{40} in the saddle-back group were longer and lower than in the control group, respectively. This result suggests that the saddle-back pattern also reflects conduction disturbances somewhat. The reason for this finding is unclear. However, it is tempting to speculate that the two morphologies, coved and saddle-back, are linked potentially at the point of arrhythmogenesis, because some patients with saddle-back pattern may have a coved pattern just before the occurrence of VF.^{14,16}

Theoretical considerations and recent experiments have suggested one possible mechanism for ST-segment elevation in the right precordial leads and arrhythmogenesis in this syndrome. Antzelevitch et al.^{2,5,6} have proposed that epicardial-endocardial heterogeneity of repolarization is responsible for both patterns of ST-segment elevation in patients with Brugada syndrome. Their mechanistic hypothesis suggests that a further rebalancing of currents leads to heterogeneous loss of the action potential dome in the epicardium but not in the endocardium, thereby creating an arrhythmogenic substrate that gives rise to phase 2 reentry. This scenario also suggests that phase 2 reentry depends critically on the duration of the abbreviated action potential. An association between sodium channel activity and Brugada syndrome has been well described. Inhibition of the sodium channel depresses the early part of the action potential, abbreviates its duration, facilitates loss of the action potential dome, and also effectively unmasks the Brugada syndrome.^{5,17-19} In addition to the above findings, the linkage of Brugada syndrome to mutations in SCN5A, the sodium channel gene, was reported.^{4,20-24} A defect in sodium channel activity is known to cause conduction disturbances. Although the heterogeneity of repolarization and conduction disturbances may be considered as alternative

explanations for arrhythmogenesis in the Brugada syndrome, they appear to have an indirect association as components favoring the mechanisms.

We speculate that the coved pattern of ST-segment elevation represents inhibited sodium channel activity; i.e., the conduction disturbances present in patients with Brugada syndrome who have the coved ST-segment elevation may reflect markedly abbreviated action potential duration in the epicardium.

ST-Segment Morphology and Life-Threatening Events

Atarashi et al.¹³ showed that the coved pattern of ST-segment elevation is very common in patients with a history of VF (85%) and in patients with symptom (syncope and VF) (73.7%) by identifying patients with the Brugada-type ECG. In addition, a case report has shown that the ECGs recorded through just the preceding and following VF demonstrated progressive change of the configuration of the ST-segment elevation from the saddle-back to the coved pattern.¹⁴ These findings suggest that the coved ST-segment elevation carries a higher risk of VF attack. In the present study, we compared the frequency of life-threatening events between two groups of patients with two distinct ECG morphologies (coved and saddle-back ST-segment elevation) retrospectively, and showed that life-threatening events were more common in the coved group than in the saddle-back group. This observation seems to support the hypothesis that the coved ST-segment elevation has greater arrhythmogenic potential. In the large multicenter study that examined the prognostic significance of Brugada syndrome by Brugada et al.,²⁵ they regarded as true Brugada patients when the coved ST-segment elevation appeared spontaneously or after administration of a Class I agent. In contrast, Priori et al.²⁶ reported that the morphology of the ST-segment elevation (i.e., coved and saddle-back patterns) was not related to cardiac events. The electrocardiographic presentations of the disease can be intermittent and both patterns of ST-segment elevation may occur in the same patients.^{3,14,16} These observations may be responsible for the difference between Priori et al.²⁶ and others. In the present study, the patients were classified by the pattern at SAECG. As a result, the more extensive conduction disturbances in patients with the

coved ST-segment elevation were associated with life-threatening events.

LIMITATIONS

There are some limitations in the present study. First, this study lacks follow-up data. Although we assessed cardiac events in patients with Brugada-type ECG, this result was not based on prospective evaluation of the risk associated with the coved ST-segment elevation. Second, we classified the patients with the morphology of ST-segment elevation at the time of SAECG. As described above, it is well known that the ST segment in Brugada-type ECG is dynamic. Third, we did not assess further examination to obtain full diagnosis of Brugada syndrome, such as genetic analysis, Class I agent administration, and so on.

CONCLUSIONS

The coved pattern of ST segment was more closely related to conduction disturbances than the saddle-back pattern in patients with Brugada-type ECG. Life-threatening events were more common in patients with the coved ST-segment elevation. Conduction disturbances in the coved pattern of ST segment may reflect a substrate of arrhythmogenesis in Brugada syndrome.

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