Noninvasive Risk Stratification of Subjects with a Brugada-Type Electrocardiogram and No History of Cardiac Arrest

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Background: Recent studies suggest that the Brugada-type electrocardiogram (ECG) is much more prevalent than the manifest Brugada syndrome. Although invasive electrophysiologic investigations have been proposed as a risk stratifier, their value is controversial, and alternative noninvasive techniques may be preferred. We sought a noninvasive strategy to detect a high-risk group in a long-term follow-up study of subjects with a Brugada-type ECG, and no history of cardiac arrest.

Methods: This study enrolled 124 consecutive subjects with a Brugada-type ECG. Prognostic indices included: age, sex, a family history of sudden death, syncopal episodes, a spontaneous coved-type ST-segment elevation, maximal magnitude of ST-segment elevation, a spontaneous change in ST segment, a mean QRS duration, maximal QT interval, QT dispersion, late potentials (LP) by signal-averaged ECG, and microvolt T-wave alternans.

Results: Of the 124 subjects, 20 consenting subjects had an implantable defibrillator before follow-up. During a 40 ± 19 -month follow-up, 12 subjects (9.7%) reached one of the endpoints (sudden death or ventricular tachyarrhythmia). Of the 12 risk indices, a family history of sudden death, syncopal episodes, a spontaneous coved-type ST-segment elevation, a spontaneous change in ST segment, and LP had significant values. In multivariate analysis, a spontaneous change in ST segment had the most significance (a relative hazard, 9.2; $P = 0.036$). Combined assessment of this index and other significant indices obtained higher positive predictive values (43–71%).

Conclusions: A spontaneous change in ST segment is associated with the highest risk for subsequent events in subjects with a Brugada-type ECG. The presence of syncopal episodes, a history of familial sudden death, and/or LP may increase its value.

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risk stratification; noninvasive strategy; signal-averaged electrocardiography; ventricular fibrillation

The Brugada syndrome¹ is an arrhythmogenic disorder associated with the high risk of sudden cardiac death due to ventricular fibrillation (VF) in subjects with a structurally normal heart. The syndrome is characterized by a pattern of right bundle branch block and ST-segment elevation in electrocardiogram (ECG) leads V₁ through V₃. Such ECG findings are much more prevalent than the manifest Brugada syndrome, with an incidence rang-

ing from 5 to 70 per 10,000 in healthy populations.^{2–7} In a large population study of the syndrome, Brugada et al.^{8–10} proposed that inducibility of sustained ventricular arrhythmias by electrophysiologic study (EPS) is a good risk stratifier to detect patients at high risk of sudden death, and that these high-risk patients may be candidates for an implantable cardioverter-defibrillator (ICD). However, Priori et al.^{11,12} have reported contrary

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results, and Eckardt et al.¹³ have raised concerns that induction of sustained ventricular arrhythmias is influenced by the stimulation protocol used. Although there is controversy about the prognostic value of EPS, two leading group of investigators have reached a consensus view that spontaneous normalization or manifestation of ST-segment elevation is a useful index for identifying patients at high risk in this syndrome. In clinical practice, non-invasive techniques for risk stratification of the syndrome are preferable to an invasive method, particularly in asymptomatic subjects with a Brugada-type ECG.

The aim of the present study was to compare 12 noninvasive indices, and to seek a noninvasive strategy to detect a high-risk group in a long-term follow-up study of subjects with a Brugada-type ECG and no history of cardiac arrest.

METHODS

Patient Population

Between April 1997 and January 2002, we enrolled 124 consecutive subjects with structurally normal hearts who had ECGs showing a pattern of right bundle branch block and ST-segment elevation ≥ 0.1 mV (either coved or saddle-back type) in leads V_1 – V_3 during sinus rhythm (Fig. 1) at three Japanese centers. The ECG pattern was identified during the investigation of syncope of unknown origin in 24 patients, during an ECG examination due to sudden death of family members in 11 subjects, and during annual health check-ups either arranged by their company or by themselves in the remaining 89 subjects. Before diagnosing Brugada-type ECGs, we excluded patients who had evidence of organic heart disease, including coronary artery disease and arrhythmogenic right ventricular cardiomyopathy. These diagnoses were based on echocardiography (all 124 subjects), coronary angiography with acetylcholine (46 subjects with symptoms or coronary risk factors), and other diagnostic equipments such as scintigraphy, helical CT scan, and magnetic resonance imaging. Therefore, all patients studied were believed to have structurally normal hearts. In addition, the ECG diagnosis was made in the absence of antiarrhythmic drugs—subjects who had an ECG diagnosis only after administration of antiarrhythmic drugs were excluded. Subjects with a history of documented life-threatening ventricular tach-

Figure 1. Twelve-lead ECG showing a Brugada-type ECG of coved type.

yarrhythmias or aborted sudden death were also excluded. Prior to enrollment, 20 consenting subjects received an ICD on our recommendation. Six subjects took class IA or IC antiarrhythmic drugs for treatment of paroxysmal atrial fibrillation, and these drugs were continued during the follow-up period. Informed consent was obtained from each subject. This study was approved by the institutional review boards of the participating institutions.

Noninvasive Indices

Prognostic noninvasive indices included: age (30–49 years), gender (men), a family history of sudden death, a previous history of syncope, a spontaneous coved-type ST-segment elevation, maximal ST-segment elevation >0.5 mV in leads V_1 – V_3 , a spontaneous change in ST segment on multiple or continuous ECG records, mean QRS duration >120 ms, maximal corrected QT (QTc) interval >440 ms,

QT dispersion >50 ms, and ventricular late potentials (LP) detected by signal-averaged ECG, microvolt-level T-wave alternans (TWA).

Analysis of ECG Parameters

Mean QRS duration, maximal QTc interval, QT dispersion, and the amplitude of ST-segment elevation were analyzed automatically using a computerized 12-lead ECG machine (FDX-6521, Fukuda Denshi Co., Tokyo, Japan). The QTD was defined as the difference between the minimal and maximal QTc intervals in any of the 12 ECG leads in which it could be reliably determined. ECGs with spontaneous ST-segment changes were obtained during regular outpatient clinic visits. The criteria for a spontaneous change in ST segment included: manifestation, augmentation, or normalization of ST-segment elevation, and a change from the saddle-back type to the coved type, or vice versa, on multiple ECG records at least three times on separate days, and at different times including after meals (lunch in most cases). In addition, visible ST-segment alternans on continuous ECG records was included in these criteria. The manifestation or augmentation of ST-segment elevation was defined as a prominent and spontaneous ST-segment elevation, without the use of antiarrhythmic drugs, displaying an elevated ST elevation ≥ 0.2 mV in leads V_1 - V_2 at its peak, followed by a negative or flat T wave, with little or no isoelectric separation.¹⁴ A spontaneous coved-type ST-segment elevation was defined as a prominent ST-segment elevation showing the pattern described above, which appeared spontaneously.

Late Potentials by Signal-Averaged ECG

The LP were analyzed using a signal-averaged ECG System (Arrhythmia Research Technology 1200EPX, Milwaukee, WI). The analysis was based on the quantitative time domain measurements of the filtered vector magnitude of the orthogonal Frank X, Y, and Z leads. Three parameters were assessed via a computer algorithm: (1) the filtered QRS duration, (2) the root mean square voltage of the terminal 40 ms in the filtered QRS complex (RMS_{40}), and (3) the duration of low amplitude signals <40 μ V in the terminal filtered QRS complex (LAS_{40}). In this study, the LP were considered to be positive when two criteria were met: $RMS_{40} < 20$ μ V and $LAS_{40} > 38$ ms.¹⁵

Microvolt T-Wave Alternans

After LP acquisition, microvolt-level TWA was analyzed using a CH2000 System (Cambridge Heart, Inc., Bedford, MA). This allows detection of microvolt electrical alternans of the T wave during an exercise test using the spectral method. The TWA was considered positive when the sustained alternans voltage was >1.9 μ V for at least 1 minute, with an alternans ratio >3.0 in any orthogonal lead, or two consecutive precordial leads, during exercise with an onset heart rate <110 beats/min.¹⁶

Follow-Up and Endpoints

Clinical follow-up was obtained once a month in subjects with symptoms and at 3- or 6-month intervals in subjects without any symptoms at the outpatient clinics of each participating institution. The endpoints were prospectively defined as sudden death and documentation of VF or polymorphic ventricular tachycardia (VT). Sudden death was defined as instantaneous, unexpected death. VF was defined as a polymorphic ventricular tachyarrhythmia with an R-R interval <200 ms (>300 beats/min) and hemodynamic decompensation, requiring electrical defibrillation for termination. Polymorphic VT was defined as polymorphic tachycardia lasting >5 seconds at a rate between ≤ 300 and >150 beats/min.

Statistical Analysis

Data are expressed as the mean $\pm$ SD. For analysis of the association between subsequent events and the 12 noninvasive risk indices, univariate and multivariate Cox regression analyses were performed. All 12 indices were included for a multivariate Cox regression analysis. Results of event-free analyses are presented with the relative hazard and 95% confidence intervals. Sensitivity, specificity, positive and negative predictive values, and predictive accuracy of event-free prediction of significant indices were also evaluated. Differences in event-free rates were determined using the Kaplan-Meier method and the log-rank test. A value for $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

The mean age of the subjects with Brugada-type ECG was 50 ± 15 years, and 51 subjects (41%) were

Figure 2. A spontaneous change of ST segment consistent with the Brugada syndrome in ECG leads V₁–V₃ taken on July 22, 1999.

aged 30–49 years; 117 men (94%) and 7 women were enrolled in the study. Twenty-six subjects (21%) had a family history of sudden death. The coved-type ST-segment elevation was observed in 107 subjects (86%) and in the remaining 17 subjects, only saddle-back-type ST-segment elevation was seen.

Electrocardiographic Data

Noninvasive ECG tests were successively done during sinus rhythm in all subjects. A spontaneous coved-type ST-segment elevation was present in 33 subjects (27%). The maximal ST-segment elevation for all subjects was 3.8 ± 1.6 mV. A spontaneous change in ST segment was observed in 41 subjects (33%); 28 subjects had manifestation, augmentation, or normalization of ST-segment elevation on multiple ECG records; 12 subjects changed from the saddle-back type to the coved type, or vice versa, and 9 subjects had visible ST-segment alternans on continuous ECG records. The manifestation/augmentation of ST-segment elevation was usually documented after a meal, as shown in Figure 2. The mean QRS duration was 108 ± 14 ms. The mean maximal QTc interval and the mean QT dispersion were 0.42 ± 0.04 and 45 ± 12 ms, re-

spectively. The mean RMS₄₀ and LAS₄₀ were 15.2 ± 9.8 μ V and 45 ± 12 ms, respectively, and LP were present in 72 subjects (58%). The mean maximal TWA voltage in any of the leads was 1.0 ± 1.4 μ V, and the TWA was present in 14 subjects (11%).

Arrhythmic Events

During a mean follow-up period of 40 ± 19 months, 12 patients (9.7%) reached one of the endpoints; 2 subjects suffered sudden death, 7 subjects had VF, and 3 subjects had polymorphic VT. In 9 out of 10 subjects with VF or polymorphic VT, arrhythmic events were recorded on the storage memory of an ICD. Of the 12 noninvasive risk indices, a family history of sudden death, a previous history of syncope, a spontaneous coved-type ST-segment elevation, a spontaneous change in ST segment, and LP had significant values ($P = 0.04$, $P = 0.003$, $P = 0.003$, $P = 0.002$, $P = 0.048$, respectively), as shown in Table 1. To test which index was most significant for the endpoints, a multivariate Cox proportional-hazard analysis was performed. The spontaneous change in ST segment had the most significant value, with a relative hazard of 9.2 (95% CI 1.2–73.5; $P = 0.036$), showing

Table 1. Association of Noninvasive Risk Variables with the Study Endpoints

Noninvasive Risk Variables	Positive, n (%)	Univariate Analysis		Multivariate Analysis	
		RH (95% CI)	P Value	RH (95% CI)	P Value
Age (30–49 years)	51 (41%)	2.0 (0.6–6.2)	0.25	3.3 (0.8–13.3)	0.09
Gender (Men)	117 (94%)	0.6 (0.1–4.5)	0.59	0.3 (0.1–3.2)	0.29
Family history of sudden death	26 (21%)	3.2 (1.0–10.2)	0.04	3.8 (0.8–17.4)	0.08
Syncopal episode	41 (33%)	9.7 (2.1–44.7)	0.003	4.9 (0.9–25.8)	0.06
Spontaneous coved-type ST-segment elevation	33 (27%)	6.3 (1.9–21.1)	0.003	1.0 (0.2–5.3)	0.99
Maximal ST-segment elevation >0.5 mV	24 (19%)	1.4 (0.4–5.1)	0.63	1.5 (0.3–9.2)	0.65
Spontaneous change in ST segment	41 (33%)	10.8 (2.4–49.7)	0.002	9.2 (1.2–73.5)	0.036
Mean QRS duration >120 ms	39 (31%)	1.4 (0.4–4.4)	0.57	0.8 (0.2–3.3)	0.75
Maximal corrected QT interval >440 ms	22 (18%)	0.4 (0.1–3.0)	0.37	0.3 (0.1–4.5)	0.37
Corrected QT dispersion >50 ms	23 (19%)	0.8 (0.2–3.9)	0.83	0.9 (0.1–11.0)	0.96
Late potentials by signal-averaged ECG	71 (57%)	7.9 (1.0–61.3)	0.048	1.4 (0.1–15.2)	0.76
Microvolt T-wave alternans	14 (11%)	1.6 (0.3–7.3)	0.55	2.5 (0.4–14.7)	0.31

n = number; RH = relative hazard; CI = confidence interval.

predictive values with a sensitivity of 82%, a specificity of 72%, and a positive predictive value of 24%, a negative predictive value of 98%, and a predictive accuracy of 73%. Figure 3 shows the Kaplan–Meier curves of arrhythmic events of this index during follow-up. When a spontaneous ST-segment change and other indices that were significant by univariate analyses were combined, positive predictive values became higher (Table 2). Subjects with a spontaneous ST-segment change, a previous history of syncope, and a family history of sudden death had the highest positive predictive value of 71% for life-threatening events during a mean follow-up period of 40 months. Since ICD treatment of asymptomatic subjects with Brugada-type ECG is controversial, the identification of a high-risk group in such subjects is important. We sought a risk stratification strategy using noninvasive risk indices. When a spontaneous ST-segment

change was combined with a family history of sudden death, a positive predictive value of 45% was obtained, with a low sensitivity of 42% and a high specificity of 95%. When a spontaneous ST-segment change was combined with LP detected by signal-averaged ECG, a positive predictive value of 43% was obtained, with a higher sensitivity of 82% and a lower specificity of 72%. Figure 4 shows the Kaplan–Meier event-free curves of combined assessment of a spontaneous ST-segment change, a history of syncope, and LP (A) and combined assessment of two indices except a history of syncope (B).

DISCUSSION

This prospective study is the first to use noninvasive risk stratification to compare multiple variables in subjects with Brugada-type ECG. The

Table 2. Predictive Values Associating Three Indices Used Alone and in Combination with the Study Endpoints

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PA (%)
Spontaneous change in ST segment (A)	82	72	24	98	73
History of syncope (B)	82	72	24	98	73
Family history of sudden death (C)	50	82	23	94	79
Late potentials by signal-averaged ECG (D)	92	46	15	98	51
(A) and (B)	75	91	47	97	90
(A) and (C)	42	95	45	94	90
(A) and (D)	82	72	43	98	88
(A) and (B) and (C)	42	98	71	94	93
(A) and (B) and (D)	75	91	56	97	92
(A) and (C) and (D)	42	95	45	94	90
(A) and (B) and (C) and (D)	42	98	71	94	93

PPV = positive predictive value; NPV = negative predictive value; PA = predictive accuracy.

Figure 3. Kaplan–Meier event-free curves of a spontaneous ST-segment change.

Figure 4. Kaplan–Meier event-free curves for combined assessment of a spontaneous ST-segment change and a family history of sudden death (A), and combined assessment of a spontaneous ST-segment change and late potentials (B).

outcome reveals that a spontaneous change in ST segment on multiple or continuous ECGs taken on separate days, and at different times, is associated with the highest risk for subsequent events in such subjects. Previous follow-up studies of the Brugada syndrome^{9,12} have shown that a spontaneous coved-type ST-segment elevation identified subjects at risk of cardiac arrest. Although a spontaneous coved-type ST-segment elevation was also an independent predictor for subsequent events in this study, a spontaneous change in ST segment could be more relevant and important for risk stratification of Brugada patients. When the subjects have a negative spontaneous ST-segment change, they may not benefit from ICD treatment, because of its high negative predictive value (98%).

In this study population, a spontaneous ST-segment change on ECG was usually seen after meals. This may reflect changes of autonomic modulation by a full stomach (i.e., an increase of vagal activity). Some investigators^{17–20} have proposed that vagal activity, as represented by heart rate variability patterns during Holter monitoring, influences a possible mechanism in the arrhythmogenesis of Brugada syndrome. Heart rate spectral analysis of Holter monitoring just before VF episodes showed a sudden rise in the HF (i.e., vagal activity), and a decrease in the low-to-high frequency (LF/HF) ratio (sympathetic activity). Nishizaki et al.²¹ have reported that high insulin secretion induced by food intake is associated with augmentation of ST-segment elevation in patients with the Brugada syndrome. It is known that insulin affects the Na^+/K^+ pump, $\text{I}_{\text{Ca,L}}$, and other channels, which might influence ST segment in the Brugada syndrome. Since sensitivity to insulin is high in patients with the Brugada syndrome, ST-segment elevation may be easily induced.

In the present study, LP by signal-averaged ECG was also a significant predictive index of life-threatening events or sudden death. We have previously reported that in a retrospective study, LP are a noninvasive risk stratifier in identifying patients at risk for ventricular tachyarrhythmias in patients with the Brugada syndrome.¹⁵ Studies of the mechanisms of ST-segment elevation in the Brugada syndrome suggest that both ventricular repolarization and depolarization abnormalities influence the arrhythmogenesis of the syndrome.^{22,23} Since LP reflect ventricular depolarization or a conduction abnormality, they may be associated with the arrhythmogenesis of the syndrome.

Combined assessment of noninvasive markers is one of the strategies in risk stratification of the disorder.²⁴ In the present study, combined assessment of a spontaneous change in ST segment, a previous history of syncope, and a family history of sudden death had the highest positive predictive value (71%) without reduction of sensitivity or specificity for the study endpoints. This combination could be useful as a noninvasive strategy to predict future life-threatening events or sudden death in subjects with a Brugada-type ECG, and to identify subjects who may benefit from ICD treatment. At present, little data is available for risk stratification of asymptomatic subjects with a diagnostic ECG. Brugada et al.^{9,10} have reported that both symptomatic and asymptomatic patients with sustained ventricular arrhythmias induced by EPS are a high-risk group, and they have recommended ICD treatment to prevent sudden death. In this study, we sought a noninvasive risk stratification strategy for asymptomatic subjects. Combined assessment of a spontaneous change in ST segment and a family history of sudden death or LP detected by signal-averaged ECG had a higher positive predictive value (45% or 43%, respectively) than those of single uses. These combinations could be useful in identifying asymptomatic patients at risk, as candidates for prophylactic ICD implantation. For screening to detect a high-risk group, a combination of a spontaneous change in ST segment and LP may be more useful, because this combination has a higher sensitivity (82%) for arrhythmic events than that of another combination (42%).

Study Limitations

In the present study, we collected 124 subjects with a Brugada-type ECG and no past history of cardiac arrest. Of the 124 subjects, only 12 (9.7%) had arrhythmic events or sudden death during a mean follow-up period of 40 ± 19 months. This sample size may be insufficient to confirm the data. A larger scale study and extension of the follow-up period would be required to confirm our findings. Since we did not have a specific short-term protocol regarding the identification of spontaneous change in ST segment, the method may be less applicable for immediate risk stratification.

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