sympathetic denervation is effective for the prevention of AF.

In heart rate variability analysis, the HF became lower and LF/HF ratio became higher from 1 week to 3 months after the PVI than those variables before the procedure,[16] and these results might represent a reduction in the parasympathetic input and augmented sympathetic activity. In our case, a transient decrease in the HF component and marked decrease in the LF/HF ratio after the PVI were noted together with a decreased incidence of AF and VT. The decrease in the LF/HF ratio after the PVI conflicts with the report by Pappone et al.[16] Makino et al.[17] demonstrated that there was a close association between the sympathetic nerve fibers and Marshall bundles that were localized to the pulmonary vein–left atrium junction, especially the area close to the left inferior pulmonary vein. Therefore, not only parasympathetic ganglions but also sympathetic nerve fibers could be eliminated by a radiofrequency energy application during the PVI. This may be the reason why our patient exhibited a decrease in the LF/HF ratio after the PVI.

Further investigation is required to understand the details of the effect of eliminating the triggering effects of pulmonary vein foci, as well as the autonomic nervous influence from the PVI on patients with CPVT. Further investigation into the role of the PVI in CPVT and its place in the therapeutic cascade needs to be determined.

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Quantitative Evaluation of Coronary Artery Wall Echogenicity by Integrated Backscatter Analysis in Kawasaki Disease

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Background: Coronary artery wall echogenicity increases on echocardiograms during the acute phase of Kawasaki disease (KD). According to this background, echogenicity of the coronary artery wall in patients with KD is quantified by using integrated backscatter (IB) analysis.

Methods: IB analysis is a quantitative method for evaluating echogenicity. We examined the value of IB in the wall of the left anterior descending coronary artery and compared it with that in adjacent intracardiac blood as a measure of background. The difference between these values is represented as corrected IB for the coronary artery wall.

Results: Corrected IB for the coronary artery wall was higher in patients with KD than in controls (KD with pre-immunoglobulin therapy vs. controls: 27.4 ± 5.3 dB vs. 22.0 ± 3.5 dB, $P < .05$) and in patients with coronary enlargement after intravenous immunoglobulin (with vs. without coronary enlargement, 29.2 ± 5.2 dB vs. 24.1 ± 5.5 dB, $P < .05$).

Conclusion: The magnitude of IB from the coronary artery wall reflects the effectiveness of immunoglobulin therapy. Furthermore, this method and its value might be useful to predict the occurrence of coronary enlargement in patients with KD. (J Am Soc Echocardiogr 2010;23:938-42.)

Keywords: Coronary artery wall, Echocardiography, Echogenicity, Integrated Backscatter Analysis, Kawasaki disease

The most serious sequela of Kawasaki disease (KD) is coronary enlargement, such as coronary aneurysm. Coronary enlargement may subsequently cause ischemic heart disease or myocardial infarction. The luminal diameters of coronary arteries are often measured using two-dimensional echocardiography,[1,2] and this method has become the clinical standard for patients with KD. Echogenicity in the coronary artery wall apparently increases during the acute phase of KD according to American Heart Association guidelines,[3] and it is considered an important factor among patients with atypical KD.[4] However, to estimate the echogenicity of the coronary artery wall is somewhat difficult.[2] Integrated backscatter (IB) analysis is a quantitative method for evaluating echogenicity, and it is applied to ultrasonographic assessment of the myocardium, arterial tissues[5-8] and coronary arterial plaques.[9] The study's objective was to determine whether coronary echogenicity is different in patients with KD versus controls, to describe the time course of changes in IB during the acute and convalescent phase of KD, and to investigate whether differences in echogenicity might identify patients at increased risk of developing coronary artery changes.

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MATERIALS AND METHODS

We enrolled 27 patients with KD (KD group) who were treated with intravenous immunoglobulin (IVIG) and 15 control patients who were examined by echocardiography for other heart diseases (non-KD group). Sixteen of the 27 patients in the KD group were male and 11 patients were female (mean age, 1.8 ± 1.2 years; range, 2 months to 4 years). The first IVIG treatment improved symptoms in 17 patients, whereas the other 10 patients required additional IVIG treatment (Table 1). The patients' treating physician decided whether the IVIG protocol was 400 mg/kg/d for 5 days or a bolus of 1 to 2 g/kg over 24 hours. The treatment strategy was considered effective when fever was decreased within 48 hours of the first IVIG. If fever continued for over 48 hours after the first IVIG treatment, then a second IVIG treatment was administered. Coronary enlargement was defined as an inside diameter of the coronary artery of greater than 3 mm determined by echocardiography. Fifteen patients with non-KD conditions (9 male and 6 female; mean age, 1.7 ± 1.2 years) served as controls. Their conditions included ventricular septal defect (n = 5), atrial septal defect (n = 3), peripheral pulmonary artery stenosis, (n = 2), patent ductus arteriosus, (n = 1), Wolff–Parkinson–

Abbreviations

IB = Integrated backscatter

IB_{BG} = Integrated backscatter for background

IB_{CA} = Integrated backscatter for coronary artery wall

IVIG = Intravenous immunoglobulin

KD = Kawasaki disease

ROI = Region of interest

White syndrome (n = 1), and innocent murmur (n = 3). During evaluation of congenital heart disease among this group, all coronary arteries evaluated by echocardiography appeared normal.

The IB of coronary artery wall tissues was determined using SONOS 5500 or SONOS 7500 echocardiography systems equipped with acoustic densitometers (Royal Philips Electronics, Amsterdam, The Netherlands) under the following standardized conditions: gain control, 50 dB; dynamic range, 75 dB; and time gain control, medial position with the lowest lateral gain control. IB images during two to three heartbeats were recorded on an optical disk at 30 frames per second, replayed off-line, and frozen when the image was suitable for determining IB, mainly at the end-systolic phase, using a minimal (11 × 11 pixels) elliptical region of interest (ROI) (Figure 1) for the echocardiography system. The value of IB was calculated in the wall of the left anterior descending coronary artery (IB_{CA}) and the background (IB_{BG}) at an intracardiac blood adjacent to the target coronary artery. The corrected IB_{CA} value represents the difference between the IB_{CA} and IB_{BG} of the coronary artery wall (Figure 1).

IB was determined in the KD group at three separate times: before the first IVIG (acute phase), within 12 hours of the last IVIG (after IVIG), and at least 30 days after onset of KD (convalescent phase) under approximately identical conditions (set in memory mode) throughout the observation, with respect to depth and location of the ROI.

To assess the reproducibility of the corrected IB_{CA} value, each IB image was stored on an optical disk, and the IB_{CA} and IB_{BG} were determined by 2 separate operators (interobserver measurement variability) and twice in the same frame by a single operator (intraobserver measurement variability).

The results for the KD (in acute phase, after IVIG, and convalescent phase) and non-KD groups are shown as means ± standard deviation. Means between the KD and non-KD groups and between any two subgroups in the KD group were statistically analyzed using an unpaired *t* test. Changes over time in the KD group were assessed using a paired *t* test. The reproducibility of inter- and intra-operator IB values was compared using Pearson's correlation coefficient and Bland–Altman analysis. A *P* value of less than .05 was considered significant.

All parents provided written, informed consent to their children undergoing additional conventional coronary artery examinations of the IB in the coronary artery wall.

RESULTS

Reproducibility of Measurement of Integrated Backscatter

The correlation coefficient of corrected IB_{CA} values from 23 image files that displayed a distinct coronary artery and the mean difference in inter-operator reproducibility between two operators were 0.64% and 2.3% ± 7.6%, respectively (Figure 2). The correlation coefficient and mean difference in intra-operator reproducibility were 0.80% and 0.7% ± 7.2%, respectively (Figure 3).

Table 1 Clinical characteristics of patients

	Coronary enlargement (+) n = 5	Coronary enlargement (−) (n = 22)	*P* value
Age (y)	1.0 ± 0.6	2.1 ± 1.2	NS
Male, n (%)	3 (60)	13 (59)	NS
Additional IVIG, n (%)	3 (60)	7 (32)	NS

IVIG, Intravenous immunoglobulin; *NS*, not significant.

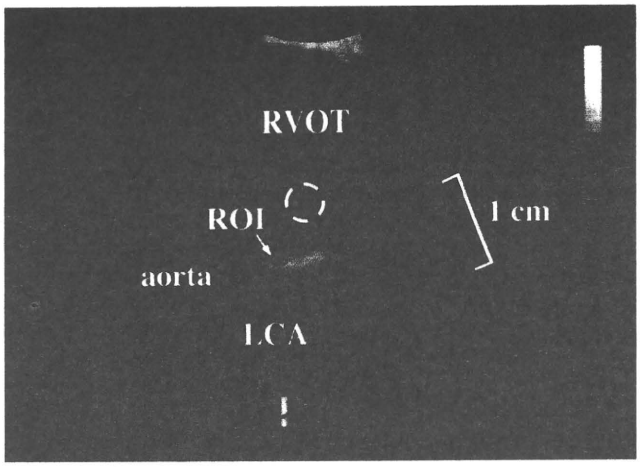

Figure 1 Method of measuring IB in coronary arterial wall. ROI used for IB measurement of the left anterior descending coronary artery is shown as a green oval. The backscatter measured from this ROI was the value of IB_{CA}. The backscatter measured from the region enclosed by the rounded broken line (blood pool) was the value of IB_{BG}. *LCA*, Left coronary artery; *RVOT*, right ventricular outflow tract; *ROI*, region of interest.

Corrected Integrated Backscatter for Coronary Artery Values in Kawasaki Disease versus Non-Kawasaki Disease

Mean corrected IB_{CA} values before and just after IVIG and during the convalescent phase were 27.4 ± 5.3 dB, 25.1 ± 5.7 dB, and 25.2 ± 5.6 dB, respectively, in the KD group, and baseline IB_{CA} was 22.0 ± 3.5 dB (range, 15.6–28.6 dB) in the non-KD group (Figure 4).

Corrected IB_{CA} values significantly differed between the KD and non-KD groups before IVIG ($P < .05$). Corrected IB_{CA} values in the KD group significantly decreased from pretreatment values just after IVIG, including additional therapy and during the convalescent phase ($P < .05$).

Corrected Integrated Backscatter for Coronary Artery in Patients with Kawasaki Disease versus Patients without Coronary Enlargement

Coronary enlargement developed in 5 of the 27 patients in the KD group (Table 2). Among the patients whose corrected IB_{CA} values decreased after first IVIG (17/27), the first IVIG was deemed effective (additional IVIG was not required) through convalescence in 14 (82%) of them and none developed coronary enlargement. On the other hand, coronary enlargement developed in 5 (50%) of 10

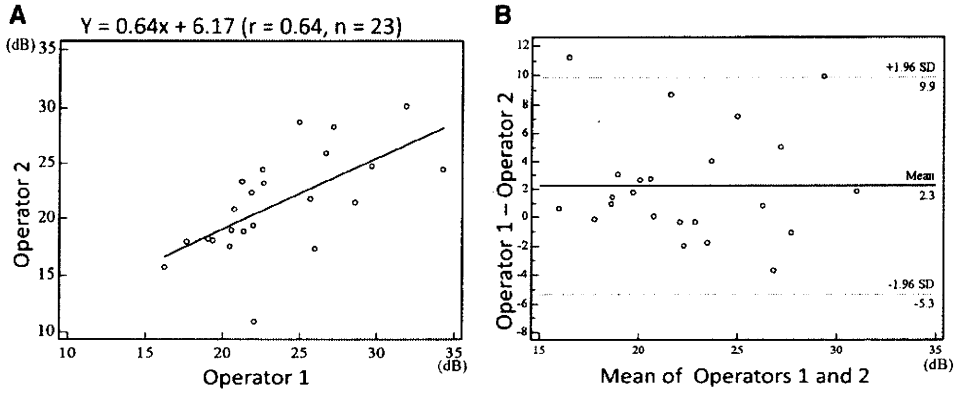

Figure 2 Assessment of inter-operator IB accuracy. These figures show the assessment of two different operators. **(A)** The linear correlation between operators 1 and 2. There was good correlation coefficient (0.64) between the two operators. **(B)** The difference in inter-operator measurement by each decibel of the values (Bland–Altman plot). *SD*, Standard deviation.

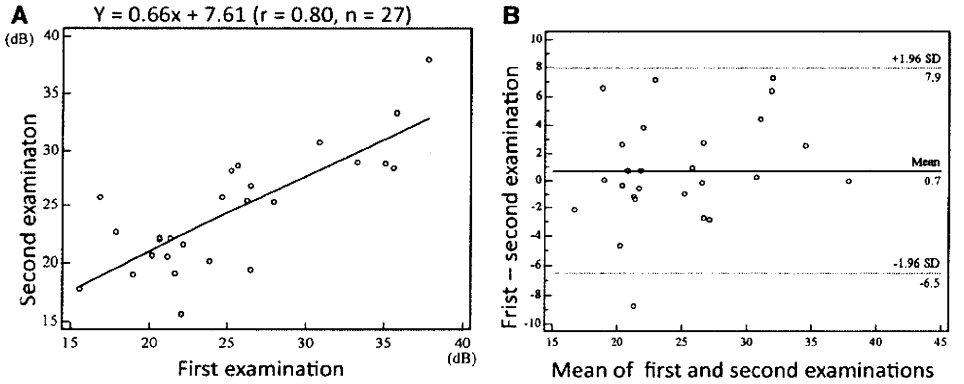

Figure 3 Assessment of intra-operator variability. These figures show the assessment of two different measurements of the same frame by the same operator. **(A)** The linear correlation between examinations 1 and 2. There was good correlation coefficient (0.80) between examinations 1 and 2. **(B)** The difference in intra-operator measurement by each decibel of the values (Bland–Altman plot). *SD*, Standard deviation.

patients whose corrected IB_{CA} values increased after the first IVIG. Among the five patients with coronary enlargement, the corrected IB_{CA} values increased beforehand in two (40%) of them and after or at the same time as coronary enlargement in three (60%) of them. The corrected IB_{CA} values for the patients with coronary enlargement were 26.5 ± 3.9 dB, 29.2 ± 5.2 dB, and 24.6 ± 4.5 dB before and after IVIG, and in the convalescent phase, respectively. These values in patients without coronary enlargement were 27.6 ± 5.6 dB, 24.1 ± 5.5 dB, and 25.2 ± 5.9 dB, respectively.

The corrected IB_{CA} values in patients with coronary enlargement significantly increased after IVIG compared with before ($P < .05$), whereas these values during the convalescent phase decreased to levels similar to those in the non-KD group (Figure 5). The corrected IB_{CA} values significantly decreased among patients without coronary enlargement after IVIG compared with that before ($P < .05$). Furthermore, the corrected IB_{CA} value in the non-KD group significantly differed from the values both before and after IVIG in patients with KD with coronary enlargement, but only from pre-IVIG values in those without coronary enlargement ($P < .05$). The course of a 3-month-old girl who was treated with IVIG on day 5 of illness when complicated coronary aneurysms developed, and in whom fever was resolved by day 6 of illness, is shown in Figure 6. The corrected IB_{CA} value increased as coronary enlargement progressed.

DISCUSSION

The relationship between the onset and the progression of coronary aneurysm during the acute phase of KD has usually been examined morphologically. The tunica media of the diseased artery is initially injured during the acute phase of KD, and this leads to intra-arterial edematous changes in arterial smooth muscle and dissects outward along the arterial wall from the tunica media along with concurrent subendothelial edema of the arterial wall arising from endothelial cells.[3] These inflammatory edematous changes during the acute phase of KD might increase the echogenicity of the arterial wall. The ultrasonic signal received by the transducer in conventional echocardiography is processed to provide readily visualized structural images with well-defined borders. However, because echogenicity is modified during this process, its value cannot be accurately determined. With IB, the reflected ultrasonic signal is recorded as raw data that avoid any influence of the echocardiographic imaging process, thus permitting accurate determinations of echogenicity.[10]

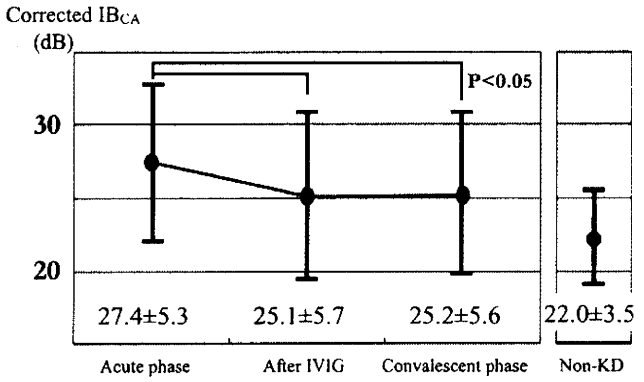

Figure 4 Corrected IB_{CA} values compared between groups with and without KD. *IVIG*, Intravenous immunoglobulin; *KD*, Kawasaki disease; *IB_{CA}*, integrated backscatter for coronary artery wall.

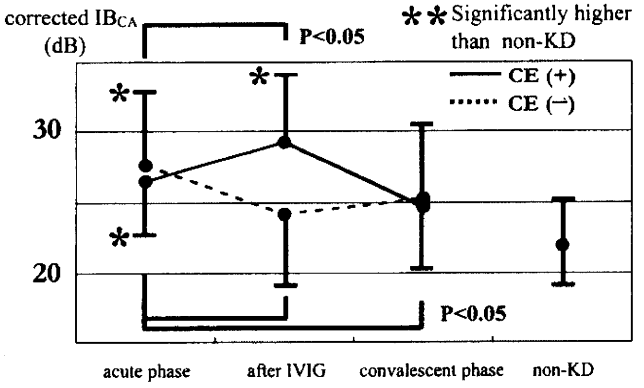

Figure 5 Corrected IB_{CA} values in patients with KD with and without coronary enlargement. *CE*, Coronary enlargement; *IVIG*, intravenous immunoglobulin; *KD*, Kawasaki disease; IB_{CA}, integrated backscatter for coronary artery wall; *dB*, decibel.

Table 2 Changes in corrected integrated backscatter for coronary artery wall values after intravenous immunoglobulin relative to coronary enlargement

Corrected IB_{CA}	Coronary enlargement (+)	Coronary enlargement (−)	*P* value
Increased	5	5	NS
Decreased	0	17	<.01

IVIG, Intravenous immunoglobulin; *IB_{CA}*, integrated backscatter for coronary artery wall; *NS*, not significant.

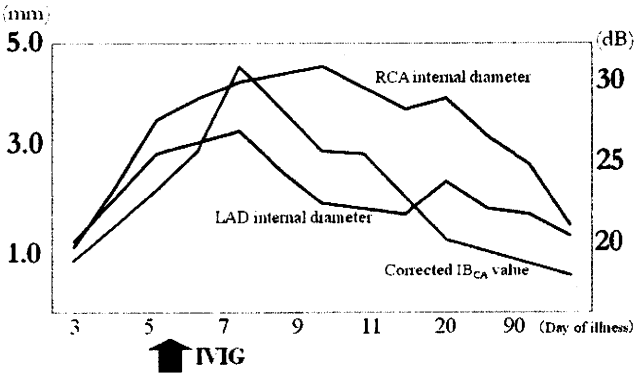

Figure 6 Time course of coronary enlargement and corrected IB_{CA} in a 3-month-old girl with KD. *IVIG*, Intravenous immunoglobulin; *KD*, Kawasaki disease; *LAD*, left anterior descending coronary artery; *RCA*, right coronary artery; *dB*, decibel; *IB_{CA}*, integrated backscatter for coronary artery wall.

When characterizing the coronary arteries, the posture of the patients, location where the transducer is applied, and equipment settings (e.g., gain control) must be carefully considered. We performed echocardiography under standardized conditions with respect to gain control, dynamic range, time gain control, lateral gain control, depth, and ROI locations for continuous assessment in absolute numbers. Because structures interposed between the artery and the body surface attenuate apparent IB for the coronary artery if IB is measured in isolation, correction with respect to a reference is required. This is usually the IB of the pericardium or intracardiac blood.[11-13] An assessment of the reproducibility of corrected IB_{CA} measurements showed that these values were closely and positively correlated. Nonetheless, some corresponding values substantially differed between operators, which underscored the difficulty of determining IB.

We found that the coronary arteries were more echogenic in patients with KD than in those without KD, and in those with coronary enlargement after IVIG during the acute phase than in those without. The corrected IB_{CA} values after IVIG decreased in patients with KD without coronary enlargement, whereas values increased significantly in patients with KD with coronary enlargement. Consequently, changes in IB values might be associated with those in coronary enlargement. These results suggest that the onset of coronary enlargement can be predicted by determining whether the corrected IB_{CA} value shortly after IVIG increases or decreases from pre-IVIG IB values. Assessing changes in corrected IB_{CA} values before and after IVIG might allow the prediction of therapeutic responses to IVIG and of the subsequent risk of coronary enlargement during the acute phase of KD. To predict coronary enlargement just after IVIG would be generally useful to select other treatment strategies, such as with pulse steroids, plasmapheresis, or anti-cytokines. Therefore, these findings might become useful clinically for predicting coronary enlargement. Notably, reproducibility depends on stabilized echocardiographic equipment and obtaining serial measurements at a site where the coronary artery is most clearly visualized.

STUDY LIMITATIONS

IB must be determined correctly in all patients under comparable conditions to carry out this type of study. However, because identical conditions cannot be ensured, we used IB values relative to the background ROI. The ROI in the coronary artery wall should be kept as small as possible; some surrounding tissues might be included in the background instead. Despite the inclusion of few patients with coronary enlargement, the difference between the IB values of patients with and without coronary enlargement was statistically significant. We could not clarify the time course for the development of coronary enlargement and how it relates to the clinical phase in terms of the increase in corrected IB_{CA} values.

The correlation coefficient between two operators was unsatisfactory ($r = 0.64$). This might have been due to the inexperience of one operator who measured IB for the first time. These findings indicate that a certain degree of operator skill is necessary to determine corrected IB_{CA} values.

CONCLUSIONS

The magnitude of IB from the coronary artery wall reflects the effectiveness of immunoglobulin therapy. Furthermore, the magnitude of IB from the coronary artery wall might be useful to predict the occurrence of coronary enlargement in patients with KD.

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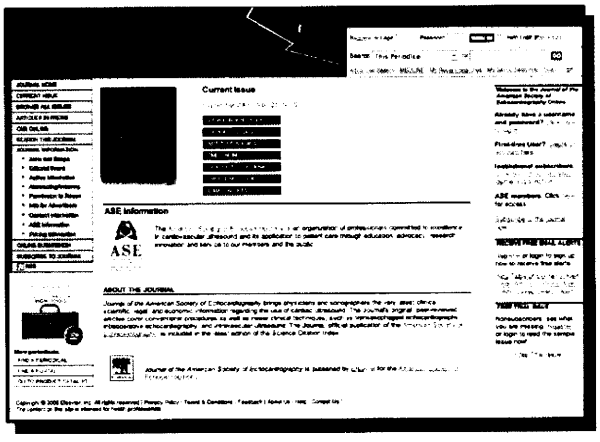

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EDITORIAL COMMENTARY

Diagnostic value of bipolar precordial leads in Brugada syndrome: More accurate, more simple, or more theoretical?

Wataru Shimizu, MD, PhD

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In 1992, Pedro and Josep Brugada first described eight patients with a history of aborted sudden cardiac death due to ventricular fibrillation (VF) and a characteristic ECG pattern, consisting of right bundle branch block and ST-segment elevation in the right precordial leads (V_1–V_3), as a distinct clinical entity.[1–8] The presence of right bundle branch block thereafter is considered not to be required for the diagnosis of Brugada syndrome, although mild-to-moderate widening of QRS duration often is observed.[4] Two specific types of ST-segment elevation (coved-type and saddleback) are observed in this syndrome, and the pattern and amplitude of ST-segment elevation often are dynamic.[9] Coved-type ST-segment elevation is more frequently recognized just before and after episodes of VF[9,10] and is reported to be related to a higher incidence of VF and sudden cardiac death.[11] The Second Consensus Report published in 2005 emphasized that type 1 ST-segment elevation, which is defined as a coved ST-segment elevation ≥ 0.2 mV at the J point with or without a terminal negative T wave, is required to diagnose Brugada syndrome.[5] Type 2 and type 3 ST-segment elevation, which have a saddleback configuration, are not diagnostic for Brugada syndrome.

ECG recordings of leads V_1 and V_2 at higher (third and second) intercostal spaces have been reported to increase the sensitivity of ECG diagnosis in detecting the Brugada phenotype.[5,12,13] We recently suggested that patients with type 1 ST-segment elevation recorded only at higher V_1–V_2 leads showed a similar prognosis for subsequent cardiac events as did recordings from standard V_1–V_2 leads.[14]

An experimental model of the Brugada syndrome using arterially perfused canine right ventricular wedge preparations[15–18] and several clinical studies[19] have suggested the cellular mechanism of Brugada phenotype, ST-segment elevation, and subsequent VF. A transient outward potassium current (I_{to})–mediated phase 1 notch of the action potential (AP) is greater in the epicardium than in the endocardium in many species, including humans.[20] A net outward shift in current active at the end of phase 1 AP (principally I_{to} and L-type calcium current [$I_{Ca\text{-}L}$]) can increase the magnitude of the AP notch, leading to loss of the AP dome (all-or-none repolarization) in the epicardium but not in the endocardium, contributing to a significant voltage gradient across the ventricular wall and producing ST-segment elevation in the ECGs recorded from wedge preparations.[15–18] In the setting of coved-type ST-segment elevation, heterogeneous loss of the AP dome (coexistence of loss of dome regions and restored dome regions) in the epicardium creates marked epicardial dispersion of repolarization, giving rise to premature beats due to phase 2 reentry, which precipitate VF.[15–18] The Brugada syndrome seems to be a clinical counterpart of the mechanism of all-or-none repolarization in the epicardial cells and phase 2 reentry-induced premature beats between adjacent epicardial cells. Therefore, higher sensitivity for ECG diagnosis of Brugada syndrome by recordings of higher V_1–V_2 leads is expected to be due to a higher or wider distribution of abnormal epicardial cells in the right ventricular outflow tract area in some patients with Brugada syndrome.

In a study reported in this issue of *Heart Rhythm*, Batchvarov et al[21] hypothesized that a bipolar precordial lead with a positive electrode at V_2 and a negative electrode at V_4 or V_5 (subtracting lead V_4 or V_5 from V_2 [$V_{2\text{–}4}$, $V_{2\text{–}5}$]) could detect with greater sensitivity the diagnostic type 1 Brugada ECG than could the standard unipolar V_2 lead. They retrospectively analyzed a digital ECG database recorded during diagnostic ajmaline testing in 128 patients with suspected Brugada syndrome. During 21 positive ajmaline tests, the type 1 pattern was observed in the higher V_2 lead (third intercostal space [V_{2h}]) during 20 tests (95.2%) and in lead V_2 during 10 tests (47.6%). The type 1 pattern appeared in lead $V_{2\text{–}4}$ or $V_{2\text{–}5}$ in all tests when it was present in V_2 and in seven tests during which it was observed in lead V_{2h} but not V_2 (total of 17 [81%] tests). In contrast, the type 1 pattern was observed in lead $V_{2\text{–}4}$ or $V_{2\text{–}5}$ during 2 (1.9%) negative tests and in 1 (0.5%) healthy subject. The authors concluded that bipolar leads $V_{2\text{–}4}$ and $V_{2\text{–}5}$ were more sensitive than the standard lead V_2 for detection of the type 1 Brugada ECG pattern but were less sensitive than the higher lead V_2. Regarding the mechanism un-

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derlying the type 1 Brugada ECG pattern in the bipolar precordial leads, the authors speculated that leads V_{2-4} and V_{2-5} reflect the voltage difference between epicardial cells in right ventricular outflow tract regions and those in left ventricular anterior regions. This may be true because left ventricular epicardial cells show an intrinsically smaller phase 1 AP notch than do right ventricular epicardial cells. The precordial bipolar leads (V_{2-4} and V_{2-5}) can be derived from standard 12-lead ECGs with the help of a software upgrade. This may be a major advantage of this method because recording of higher V_1–V_2 leads would require an ECG recorder capable of simultaneous acquisition of 14 leads. The clinical significance of the precordial bipolar leads can be meaningfully established in relation to the presence of symptoms or arrhythmic events. It is possible that a much larger number of ECG recordings will be investigated in retrospective fashion to establish the diagnostic value of the precordial bipolar leads (V_{2-4} and V_{2-5}) in patients with Brugada syndrome. A prospective study would be required to confirm the prognostic value of the precordial bipolar leads.

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Neurally Mediated Syncope as a Cause of Syncope in Patients With Brugada Electrocardiogram

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Neurally Mediated Syncope in Brugada Syndrome. ***Introduction:*** **Patients with type 1 Brugada electrocardiogram (ECG) and an episode of syncope are diagnosed as symptomatic Brugada syndrome; however, all episodes of syncope may not be due to ventricular tachyarrhythmia.**

Methods and Results: **Forty-six patients with type 1 Brugada ECG (all males, 51 ± 13 years, 29 spontaneous, 17 Ic-drug induced), 20 healthy control subjects (all males, 35 ± 11 years), and 15 patients with suspected neurally mediated syncope (NMS; 9 males, 54 ± 22 years) underwent the head-up tilt (HUT) test. During the HUT test, 12-lead ECGs were recorded in all patients, and the heart rate variability was investigated in some patients. Sixteen (35%) of 46 patients with Brugada ECG, 2 (10%) of 20 control subjects, and 10 (67%) of 15 patients with suspected NMS showed positive responses to the HUT test. Although no significant differences were observed in HUT-positive rate among Brugada patients with documented VT (7/14; 50%), syncope (5/19; 26%) and asymptomatic patients (4/13; 31%), the HUT-positive rate was significantly higher in patients with documented VT (50%) and those with VT or no symptoms (11/27, 41%) compared to that in control subjects (10%) ($P < 0.05$). Augmentation of ST-segment amplitude (≥0.05 mV) in leads V1-V3 was observed in 11 (69%) of 16 HUT-positive patients with Brugada ECG during vasovagal responses, and was associated with augmentation of parasympathetic tone following sympathetic withdrawal.**

Conclusion: **Thirty-five percent of patients with Brugada ECG showed vasovagal responses during the HUT test, suggesting that some Brugada patients have impaired balance of autonomic nervous system, which may relate to their syncopal episodes.** *(J Cardiovasc Electrophysiol, Vol. 21, pp. 186-192, February 2010)*

autonomic nervous system, Brugada syndrome, head-up tilt test, syncope, sudden death

Introduction

Brugada syndrome is characterized by ST-segment elevation in the right precordial leads V1 through V3 and an episode of ventricular tachyarrhythmia (VT) in the absence of structural heart disease.[1-3] In patients with Brugada syndrome, syncopal episodes are generally thought to be due to VT; however, all episodes of syncope may not be owing to VT events. Neurally mediated syncope (NMS) is 1 of the causes of syncope in general population, and it refers to a reflex response that some triggering factors give rise to arterial vasodilatation associated with relative or absolute bradycardia.[4] In general, the overall prognosis in patients with NMS is quite favorable.[4] On the other hand, the precise cause of syncope in patients with Brugada syndrome is difficult to determine. Therefore, the therapeutic strategy for Brugada patients with syncope is often problematic. The aim of this study was to evaluate the possibility of NMS as a cause of syncope in patients with Brugada electrocardiogram (ECG).

Methods

Patients Population

The study population consisted of 46 consecutive patients with type 1 Brugada ECG who were admitted to the National Cardiovascular Center, Suita, Japan, between May 2004 and March 2006 (all males, ages 26 to 77; mean 51 ± 13 years, 29 spontaneous, 17 Ic-drug induced), 20 healthy control subjects (all males, 35 ± 11 years), and 15 patients suspected of NMS (9 males, 54 ± 22 years). Ethical approval was obtained from the Institutional Review Committee of our hospital, and all patients and control subjects gave their informed, written consent before participation. The control subjects and the patients with suspected NMS showed no structural heart diseases, normal physical examination results, and normal 12-lead ECGs, and received no drug treatment affecting the sympathetic nervous system. Type 1 Brugada ECG was defined as a coved type ST-segment elevation of ≥ 0.2 mV at

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J point observed in more than 1 of the right precordial leads (V1 to V3) in the presence or absence of a sodium channel blocker.[2]

Head-Up Tilt Test

The HUT test was performed in the afternoon after 4 hours of fasting in a quiet and comfortable room equipped for cardiopulmonary resuscitation. All patients were allowed to lie on an electrically controlled tilt table an intravenous line containing 5% dextrose was inserted into 1 arm, and allowed to rest in supine position for at least 10 minutes. A positive HUT test was defined by the development of syncope or presyncope associated with relative bradycardia (≥20% decrease in heart rate compared with baseline) or hypotension (systolic blood pressure <80 mmHg). Presyncope was defined as the induction of symptoms of imminent syncope, and syncope was defined as sudden transient loss of consciousness. Positive response to the HUT test was classified into 3 types owing to hemodynamic status, such as vasodepressor type (hypotension without significant bradycardia), cardioinhibitory type (bradycardia without associated hypotention), and mixed type (hypotension followed by bradycardia).[4] At first, we performed passive tilt (Control-Tilt) at an angle of 70 degrees for 30 minutes. When Control-Tilt was negative, sublingual nitroglycerin (NTG) spray 0.3 mg was administered, and the test was continued for 15 minutes (NTG-Tilt). The endpoint of each tilt test was the time when patients showed positive responses or the completion of HUT-protocol.

Parameters Measured During the Head-Up Tilt Test

Heart rate and blood pressure

Heart rate was monitored, and cuff blood pressure was measured by electrosphygmomanometry with a microphone placed over the brachial artery to detect Korotkoff sounds every minute (STBP-780, Colin Electronics, Komaki, Japan) in all patients during the HUT test.

ST-segment amplitude in the right precordial leads

Twelve-lead ECGs were recorded every 1 minute during the HUT test, and the changes of ST-segment amplitude in the right precordial leads (V1-V3) were analyzed (ML-6500, Fukuda-denshi, Tokyo, Japan) in all patients during the HUT test.

Heart rate variability

Six-lead ECGs from the Task Force Monitor (CNSystem, Graz, Austria)[5-7] were measured for beat-to-beat heart rate and consecutive R-R intervals in 10 patients with Brugada ECG (4 documented VT, 5 syncopal episode only, and 1 asymptomatic), 9 control subjects, and 5 patients with suspected NMS. The heart rate variability (HRV) was investigated by a power spectral analysis delineating the low-frequency component (LF; 0.04–0.15 Hz) and the high-frequency component (HF; 0.15–0.40 Hz).[8] We analyzed the normalized unit of the HF components (%) calculated automatically (HF/power spectral density-very low-frequency component [0–0.04 Hz] × 100)[8,9] and the LF/HF ratio. The HF indicates the tone of the parasympathetic nervous system, and the LF/HF ratio indicates the sympathovagal balance.

Statistical Analysis

Numerical values were expressed as means ± SD unless otherwise indicated. Comparisons of parameters between 2 groups were made using the unpaired Student *t*-test. Comparisons of parameters among 3 groups were made with a one-way analysis of variance (ANOVA), followed by the Scheffe's multiple-comparison test. Categorical variables were compared using a chi-square analysis using the Yate's correction or Fisher exact test if necessary. An overall chi-square test for a 2 × n table was performed when comparisons involved >2 groups. A P-value < 0.05 was considered significant.

Results

Clinical Characteristics

The clinical characteristics of 46 patients with Brugada ECG and 15 patients with suspected NMS are shown in Table 1. The patients with Brugada ECG were divided into 3 groups: (1) 14 patients with documented VT; (2) 19 patients with syncopal episodes only; and (3) 13 asymptomatic patients. No significant differences were observed in age, incidence of spontaneous type 1 ECG, family history of sudden cardiac death (SCD), induced ventricular fibrillation during electrophysiologic study (EPS), and *SCN5A* mutation. Implantable cardioverter-defibrillator (ICD) was implanted more frequently in patients with documented VT. The triggers of VT and/or syncope are also shown in Table 1. Seventy-nine percent of VT episodes occurred during sleep or at rest in patients with documented VT ($P < 0.0001$ vs the patients with syncopal episodes only and suspected NMS). On the other hand, in patients with syncopal episodes only, 15% of syncopal episodes occurred after urination, 21% during standing, and 21% after drinking alcohol, which seemed to be similar patterns in patients with suspected NMS. Based on the clinical description of the syncopal events, 16 (84%) of 19 Brugada patients with syncopal episodes were suspected to have NMS. Syncopal episodes seemed to be due to VT in 1 of the remaining 3 patients.

Positive Response to the Head-Up Tilt Test

Comparison of the positive responses to the HUT test between 46 patients with Brugada ECG and 20 control subjects along with 15 patients with suspected NMS are shown in Table 2. Sixteen (35%) of 46 patients with Brugada ECG showed positive responses. Positive responses were developed in 1 (2%) of 46 patients during Control-Tilt and in 15 (33%) of 45 patients during NTG-Tilt, and the mixed type was predominant (94%). In patients with Brugada ECG, there were no significant differences in the incidence of positive responses among patients with documented VT (50%), those with syncopal episodes only (26%), and asymptomatic patients (31%). No significant differences were observed in the type of positive responses between the 3 groups. The mixed type was predominant (100%, 100%, and 75%, respectively), and cardioinhibitory type was not observed in all 3 groups. Two (10%) of 20 control subjects and 10 (67%) of 15 patients with suspected NMS showed positive responses. The HUT-positive rate was not significantly different between all 46 patients with Brugada ECG, 20 control subjects and 15 subjects with suspected NMS (35% vs 10% vs 67%);

TABLE 1
Clinical Characteristics of Patients with Brugada Electrocardiogram and Suspected NMS

	Documented VT (n = 14)	Syncopal Episodes only (n = 19)	Asymptomatic (n = 13)	Suspected NMS (n = 15)
Age (years)	50 ± 15	51 ± 12	52 ± 14	54 ± 22
Spontaneous type 1 ECG	10 (71)	9 (47)	10 (77)	–
Family history of SCD	4 (29)	4 (21)	4 (31)	–
Induced VF during EPS	10/12 (83)	15/18 (83)	8/11 (73)	–
SCN5A mutation	1 (7)	3 (16)	0 (0)	–
ICD implantation	14 (100)	13 (68)*	7 (54)*	–
Triggers of syncope				
During sleeping or at rest	11 (79)	1 (5)*	–	0*
After urination	0	3 (15)	–	1 (7)
Prolonged standing at attention	0	4 (21)	–	4 (27)
After drinking alcohol	0	4 (21)	–	6 (40)
After meal	1 (7)	0	–	0
After exertion	0	2 (11)	–	2 (13)
After sudden unexpected pain	0	2 (11)	–	0
During driving	0	1 (5)	–	0
Others	2 (14)	2 (11)	–	2 (13)

Values are mean ± SD for age, and expressed as frequency (%). *P < 0.05 vs documented VT group. ECG = electrocardiogram; EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator; NMS = neurally mediated syncope; SCD = sudden cardiac death; VT = ventricular tachyarrhythmias; VF = ventricular fibrillation.

however, the HUT-positive rate was significantly higher in 14 patients with documented VT (50%) and 27 patients with VT or no symptoms (41%) compared to that in control subjects (10%) (P = 0.03, P = 0.04, respectively). The HUT-positive rate in 19 Brugada patients with syncopal episodes (26%) was significantly lower than that in 15 patients with suspected NMS (P = 0.04), although the syncopal episodes in 84% of the 19 patients were suspected to be due to NMS. Positive responses to the HUT test were more frequency observed in 15 patients with suspected NMS compared to those in 20 control subjects (10/15 vs 2/20; P < 0.001).

Comparison of the clinical characteristics between 16 HUT-positive patients and 30 HUT-negative patients with Brugada ECG were shown in Table 3. No significant differences were observed in cardiac events, such as documented VT or syncope. Furthermore, there were no significant differences in the clinical characteristics, such as age, spontaneous type 1 ECG, a family history of SCD, inducibility of ventricular fibrillation during EPS, *SCN5A* mutation, and ICD implantation.

Response of Heart Rate and ST-Segment Amplitude

In patients with Brugada ECG, the heart rate was increased by 12 ± 9 beats/min during Control-Tilt, and by 24 ± 14 beats/min during NTG-Tilt. As the heart rate was increased, decrease of ST-segment amplitude of ≥ 0.05 mV from baseline in the right precordial leads was observed in 11 (24%) of 46 patients during Control-Tilt (−0.14 ± 0.08 mV), and in 19 of 45 (42%) patients during NTG-Tilt (−0.15 ± 0.10 mV) (Fig. 1C). However, augmentation of ST-segment amplitude of ≥ 0.05 mV in the right precordial leads was observed just before and after positive responses to the HUT test in 11 (69%) of 16 HUT-positive patients (0.10 ± 0.06 mV) (Figs. 1D and E). These significant ST-segment augmentation was observed in 1 patient during Control-Tilt (documented VT), and 10 patients during NTG-Tilt (5 documented VT, 2 syncopal episodes only, 3 asymptomatic), respectively. On the other hand, augmentation of the ST-segment amplitude of ≥ 0.05 mV was 2 (7%) of 30 HUT-negative patients during NTG-Tilt (1 documented VT, 1 syncopal episodes only). As a result, the average ST-segment augmentation was

TABLE 2
Responses to Head-Up Tilt Test in Patients with Brugada Electrocardiogram, Control Subjects, and Patients with Suspected NMS

	All (n = 46)	Documented VT (n = 14)	Syncopal Episodes Only (n = 19)	Asymptomatic (n = 13)	Brugada ECG with VT or No Symptoms (n = 27)	Control Subjects (n = 20)	Suspected NMS (n = 15)
Age (years)	51 ± 13*	50 ± 15*	51 ± 12*	52 ± 14*	51 ± 14*	35 ± 11	54 ± 22*
Positive response	16 (35)	7 (50)*	5 (26)†	4 (31)	11 (41)*	2 (10)	10 (67)*
Control-tilt	1/46 (2)	1/14 (7)	0/19 (0)	0/13 (0)	1/27 (4)	0/20 (0)	0/15 (0)
NTG-tilt	15/45 (33)†	6/13 (46)*	5/19 (26)†	4/13 (31)	10/26 (38)	2/20 (10)	10/15 (67)*
Type of positive response							
Vasodepressive	1/16 (6)	0	0	1/4 (25)	1/11 (9)	0	1/10 (10)
Cardioinhibitory	0	0	0	0	0	0	0
Mixed	15/16 (94)	7/7 (100)	5/5 (100)	3/4 (75)	10/11 (91)	3 (100)	9/10 (90)

Values are expressed as frequency (%). *P < 0.05 vs control subjects, †P < 0.05 vs suspected NMS. ECG = electrocardiogram; NMS = neurally mediated syncope; NTG = nitroglycerin; VT = ventricular tachyarrhythmias.

TABLE 3
Comparison of Clinical Characteristics Between Head-up Tilt-Positive Patients and Head-up Tilt-Negative Patients

	HUT-Positive (n = 16)	HUT-Negative (n = 30)	P-value
Age (years)	52 ± 13	50 ± 14	0.58
Documented VT	7 (44)	7 (23)	0.15
Syncope only	5 (31)	14 (47)	0.49
Asymptomatic	4 (25)	9 (30)	0.99
Spontaneous type 1 ECG	11 (69)	18 (60)	0.79
Family history of SCD	4 (25)	8 (27)	1.0
Induced VF during EPS	13/15 (87)	20/26 (77)	0.72
SCN5A mutation	1 (6)	3 (10)	1.0
ICD implantation	14 (88)	24 (80)	0.82

Values are expressed as frequency (%). ECG = electrocardiogram; EPS = electrophysiological study; HUT = head-up tilt test; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; VT = ventricular tachyarrhythmias; VF = ventricular fibrillation.

significantly larger in 16 HUT-positive patients than in 30 HUT-negative patients at similar heart rate (0.06 ± 0.06 mV vs −0.04 ± 0.06 mV, $P < 0.0001$). No ventricular arrhythmias were induced during the HUT test in any patients with Brugada ECG. The ST-segment augmentation was not observed during the HUT test in any control subjects (−0.02 ± 0.02 mV, $P < 0.0001$ vs 16 HUT-positive Brugada patients) and patients with suspected NMS (−0.02 ± 0.04 mV, $P < 0.001$ vs 16 HUT-positive Brugada patients; Fig. 2).

Heart Rate Variability and ST-segment Amplitude

Positive responses during NTG-Tilt were observed in 4 (40%) of 10 patients with Brugada ECG, in 1 (11%) of 9 control subjects, and in 4 (80%) of 5 patients with suspected NMS in whom the HRV was monitored. The autonomic activities in a representative NTG-Tilt-positive patient with Brugada ECG and those with suspected NMS are shown in Figure 3A and B, respectively. Before positive responses to the HUT test, sympathetic activity (LF/HF ratio) dramatically increased; and then, sympathetic withdrawal occurred immediately. Thereafter, parasympathetic nerve activity (the normalized unit of the HF components) gradually increased. The similar pattern of augmented parasympathetic nerve activity following sympathetic withdrawal during positive responses to the HUT test was observed in all 9 HUT-positive patients. The patterns of HRV were not different among the HUT-positive patients with Brugada ECG, the HUT-positive control subjects, and the HUT-positive patients with suspected NMS. In 3 (75%) of 4 HUT-positive patients with Brugada ECG, the LF/HF ratio decreased and the HF component increased gradually toward the maximum ST-segment elevation just before and after positive response for the HUT test (Fig. 3A), but ST-segment was decreased in patients with NMS (Fig. 3B).

Discussion

In this study, 35% of patients with Brugada ECG showed vasovagal responses during the HUT test regardless of the presence VT or syncope. The HUT test was also positive in 41% among only Brugada patients with documented VT or no symptoms. During vasovagal response, ST-segment augmentation in the right precordial leads (V1-V3) was observed in 11 (69%) of 16 HUT-positive patients with Brugada ECG, but no ventricular arrhythmias were induced in any HUT-positive patients.

Neurally Mediated Syncope as a Cause of Syncope in Brugada Syndrome

Several case reports have described patients exhibiting clinical phenotype of both Brugada syndrome and NMS.[10-12]

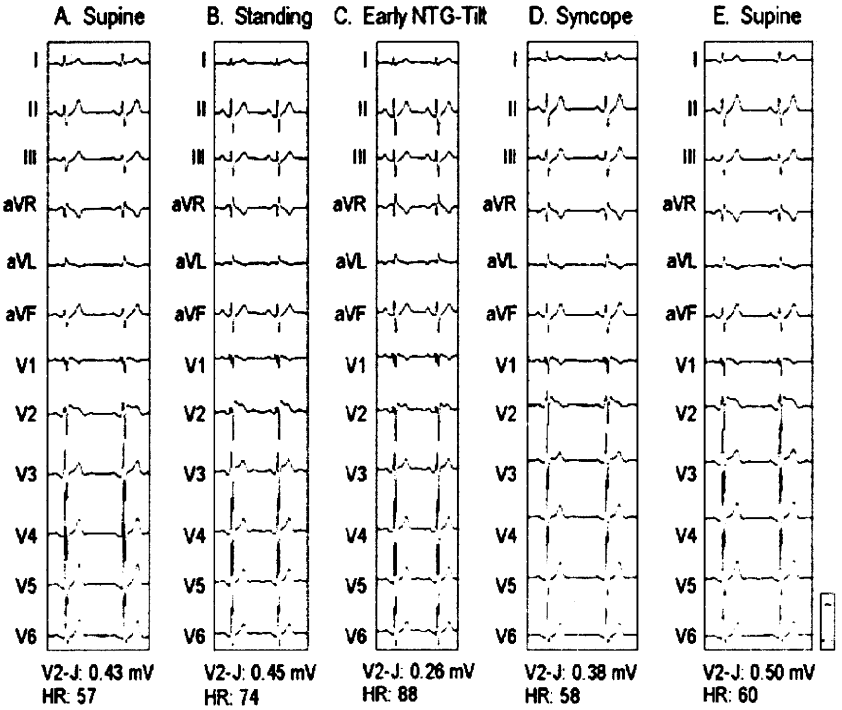

Figure 1. *The12-leads electrocardiogram (ECG) during head-up tilt test in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada ECG at supine position (A), at standing position (B), at early phase of NTG-Tilt (C), at syncope (D), and at supine position following syncope (E). The ST-segment elevation was decreased from 0.45 mV to 0.26 mV at early phase of NTG-Tilt as the heart rate was increased (C), while it was augmented to 0.38 mV at syncope (D), and to 0.50 mV at supine position following syncope (E).*

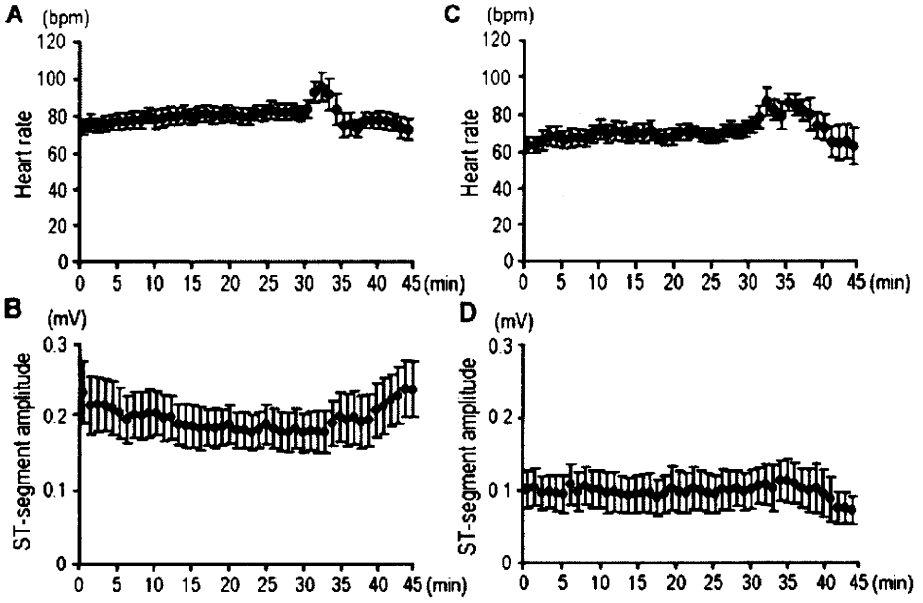

Figure 2. *Response of the heart rate and ST-segment amplitude during the head-up tilt (HUT) test in 16 HUT-positive patients with Brugada electrocardiogram (ECG) (A, B) and in 10 HUT-positive patients with suspected neurally mediated syncope (NMS) (C, D). At first, the passive tilt (Control-Tilt) was performed for 30 minutes (0–30 minutes). When Control-Tilt was negative, nitroglycerin tilt was continued for 15 minutes (30–45 minutes). The responses of heart rate during positive responses to the HUT test were similar in patients with Brugada ECG (A) to those in patients with suspected NMS (C). In patients with Brugada ECG, ST-segment in lead V2 was augmented before and after positive responses to the HUT test (B), but not in those with suspected NMS (D).*

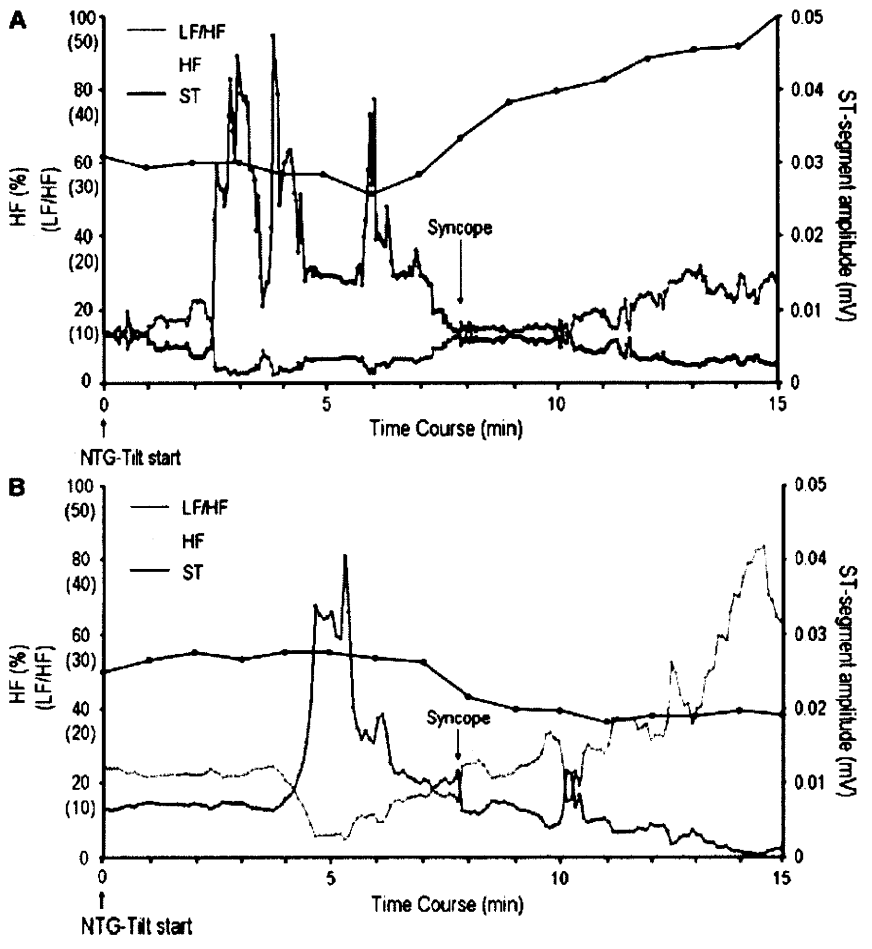

Figure 3. *Autonomic responses during head-up tilt (HUT) test. The autonomic activities in a representative nitroglycerin (NTG)-Tilt-positive patient with type 1 Brugada electrocardiogram (ECG) (A) and those in a representative NTG-Tilt-positive patient with suspected NMS (B). Before tilt-induced syncope, sympathetic activity (LF/HF ratio) dramatically increased; and then, sympathetic withdrawal occurred immediately. Thereafter, parasympathetic nerve activity (the normalized unit of the HF components) gradually increased. In the HUT-positive patient with Brugada ECG, ST-segment augmentation in lead V2 was observed just before and after positive responses, and the LF/HF ratio decreased and the HF component increased gradually toward the maximum ST-segment elevation (A). In contrast, in the HUT-positive patient with suspected NMS, ST-segment amplitude in lead V2 was decreased gradually after positive responses (B).*

It is well known that the autonomic nervous system plays an important role on the arrhythmogenesis of Brugada syndrome. Previous studies showed that the withdrawal of sympathetic activity and the sudden rise in vagal activity was an important triggering factor of ventricular fibrillation.[13-15] Similarly, it has been presumed that parasympathetic tone increase during NMS events in patients with Brugada ECG. Recent basic study showed that *SCN5A*, a major responsible gene in Brugada patients, is expressed not only in the myocardial cells but also in intracardiac ganglia.[16] Makita *et al.* also demonstrated a novel nonsense mutation in *SCN5A* gene in a patient with Brugada syndrome who had been diagnosed as NMS.[17] These results suggested that the abnormal regulation or imbalance of autonomic nervous system may exist regardless of the presence or absence of cardiac events in patients with Brugada ECG.

ST-Segment Elevation in the Precordial Leads During the HUT Test in Patients with Brugada ECG

In Brugada syndrome, spontaneous augmentation of ST-segment elevation occurred along with an increase in vagal activity, especially just before and after the occurrence of ventricular fibrillation.[14] The ST-segment elevation is also known to be modulated by exercise,[18] pharmacological interventions that interact with automatic nervous activities,[19] or taking meals associated with glucose-induced insulin levels.[20] In this study, ST-segment augmentation in the right precordial leads was observed just before and after positive responses to the HUT test in two-thirds (69%) of the HUT-positive patients with Brugada ECG but only in 7% of the HUT-negative patients. In patients with Brugada ECG, the preceding increase of sympathetic nerve activity during the HUT test may cause augmentation of ICa-L, resulting in attenuation of ST-segment elevation.[19] Subsequent augmentation of parasympathetic nerve activity during the HUT test may decrease of ICa-L, and increase Ito, thus augmenting ST-segment amplitude.

Clinical Implication

The second consensus report suggested that symptomatic patients displaying type 1 Brugada ECG (either spontaneous or after class Ic drugs) who present with aborted sudden death should undergo ICD implantation.[3] ICD implantation is also recommended in patients with syncope, seizure, or nocturnal agonal respiration, after noncardiac causes of these symptoms have been carefully ruled out.[3] Needless to say, the ECG recording during syncope is the only convincing way to rule in or out VT during syncope, and only clinical judgment can be used to guide diagnostic and therapeutic decisions. However, in patients with Brugada syndrome, there is an abnormal regulatory imbalance of the autonomic nervous system that may be a common denominator to both syncope and ventricular fibrillation.

Limitations

The control subjects were significantly younger than patients with Brugada ECG or those with suspected NMS. However, it is reported that the positive rate of NTG-Tilt in the elderly was comparable to that seen in younger subjects.[21] Therefore, lower incidence of positive rate of the HUT test in the control subjects than that in the other 2 groups was not due to the relevant difference of age. The incidence of spontaneous type 1 ECG and the positive rate of the HUT test are smaller in Brugada patients with syncope episodes only than in those with documented VT or asymptomatic patients; however, statistical significance was not observed between the 3 groups.

Conclusions

Thirty-five percent of patients with Brugada ECG showed vasovagal responses during the HUT test. The HUT test was also positive in 41% among only Brugada patients with documented VT or no symptoms. During vasovagal response, ST-segment augmentation in the right precordial leads was observed in 69% of the HUT-positive Brugada patients, but no ventricular arrhythmias were induced. These data suggest that some Brugada patients have impaired balance of autonomic nervous system, which may relate to their syncopal episodes. Additional studies including a large number of subjects are needed to validate our findings and possibly evaluate the role of the HUT test in risk stratification of patients with Brugada ECG.

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Augmented ST-Segment Elevation During Recovery From Exercise Predicts Cardiac Events in Patients With Brugada Syndrome

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Objectives The goal of this study was to evaluate the prevalence and the clinical significance of ST-segment elevation during recovery from exercise testing.

Background During recovery from exercise testing, ST-segment elevation is reported in some patients with Brugada syndrome (BrS).

Methods Treadmill exercise testing was conducted for 93 patients (91 men), 46 ± 14 years of age, with BrS (22 documented ventricular fibrillation, 35 syncope alone, and 36 asymptomatic); and for 102 healthy control subjects (97 men), 46 ± 17 years of age. Patients were routinely followed up. The clinical end point was defined as the occurrence of sudden cardiac death, ventricular fibrillation, or sustained ventricular tachyarrhythmia.

Results Augmentation of ST-segment elevation ≥0.05 mV in V_1 to V_3 leads compared with baseline was observed at early recovery (1 to 4 min at recovery) in 34 BrS patients (37% [group 1]), but was not observed in the remaining 59 BrS patients (63% [group 2]) or in the 102 control subjects. During 76 ± 38 months of follow-up, ventricular fibrillation occurred more frequently in group 1 (15 of 34, 44%) than in group 2 (10 of 59, 17%; p = 0.004). Multivariate Cox regression analysis showed that in addition to previous episodes of ventricular fibrillation (p = 0.005), augmentation of ST-segment elevation at early recovery was a significant and independent predictor for cardiac events (p = 0.007), especially among patients with history of syncope alone (6 of 12 [50%] in group 1 vs. 3 of 23 [13%] in group 2) and among asymptomatic patients (3 of 15 [20%] in group 1 vs. 0 of 21 [0%] in group 2).

Conclusions Augmentation of ST-segment elevation during recovery from exercise testing was specific in patients with BrS, and can be a predictor of poor prognosis, especially for patients with syncope alone and for asymptomatic patients. (J Am Coll Cardiol 2010;56:1576–84) © 2010 by the American College of Cardiology Foundation

Brugada syndrome (BrS) is recognized as a clinical syndrome that leads to sudden cardiac death (SCD) in middle-aged persons due to ventricular fibrillation (VF) (1). Brugada syndrome is defined by a distinct 12-lead electrocardiogram (ECG) pattern in precordial leads (V_1 to V_3) presenting coved-type ST-segment elevation. Both depolarization and repolarization hypotheses have been reported for the pathogenesis of phenotype in BrS (2–5). Although several indexes have been reported as predictive factors of VF occurrence (6), the recent largest series of BrS patients suggested that there were no reliable predictors of cardiac events except for prior symptoms and spontaneous type 1 ECG (7). However, risk stratification remains disputable, especially for BrS patients without documented VF episodes.

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Autonomic function has been suggested to relate to the occurrence of VF in BrS. It has also been shown that ST-segment elevation in patients with BrS was augmented

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by selective stimulation of muscarinic receptors but mitigated by beta-adrenergic stimulation (8). Heart rate during exercise testing is considered as 1 parameter to evaluate cardiac autonomic function (9). Sympathetic withdrawal and parasympathetic activation occur at early recovery after exercise (10), which are expected to augment ST-segment elevation directly by inhibition of calcium-channel current or by decreasing heart rate (5,11). Two cases of BrS were reported in which ST-segment was augmented during and after exercise (12). Amin et al. (13) recently assessed the ECG responses to exercise in BrS patients with and without *SCN5A* mutations and control subjects. They reported that exercise resulted in an increase of peak J-point amplitude in all groups, including control subjects, and more QRS widening in BrS patients with *SCN5A* mutation. The peak J-point amplitude measured by Amin et al. (13) is thought to represent the depolarization parameter as QRS duration, or at least the combined parameter of both depolarization and repolarization. Therefore, in the present study, we measured several points of ST-segment as a repolarization parameter rather than a depolarization parameter, and tried to investigate the relationship between augmented ST-segment elevation during recovery from exercise testing and prognosis of BrS patients. We also evaluated parasympathetic reactivation by using heart rate recovery (HRR), which is defined as heart rate decay in the first minute after exercise cessation, and its relation with ST-segment change.

Methods

Study population. The study population consisted of 93 consecutive Japanese patients with BrS (91 males; mean age 46 ± 14 years) admitted to the National Cerebral and Cardiovascular Center in Suita, Japan, between 1994 and 2006. Ventricular fibrillation was documented in 22 BrS patients, syncope alone in 35 patients, and the remaining 36 patients were asymptomatic. As control subjects, 102 age-, sex-, and QRS duration-matched healthy subjects were randomly selected from persons who underwent treadmill exercise testing between 2002 and 2007 (97 males; mean age 46 ± 17 years). They included 55 normal subjects with normal QRS duration (<100 ms), 21 with incomplete right bundle branch block (RBBB) (100 ms ≤QRS duration <120 ms), and 26 with complete RBBB (120 ms ≤QRS duration) but without structural heart disease or any ventricular arrhythmias.

Brugada syndrome was diagnosed when a coved ST-segment elevation (≥0.2 mV at J-point) was observed in >1 of the right precordial leads (V_1 to V_3) in the presence or absence of a sodium-channel–blocking agent, and in conjugation with 1 of the following: documented VF, polymorphic ventricular tachycardia, family history of SCD <45 years of age, family history of BrS, inducibility of VF with programmed electrical stimulation, syncope, or an nocturnal agonal respiration (6). Structural heart diseases were carefully excluded by history taking, physical examinations, chest roentgenogram, ECG, and echocardiogram.

Abbreviations and Acronyms

AF = atrial fibrillation
BrS = Brugada syndrome
ECG = electrocardiogram
EPS = electrophysiologic study
HRR = heart rate recovery
ICD = implantable cardioverter-defibrillator
RBBB = right bundle branch block
RVOT = right ventricular outflow tract
SCD = sudden cardiac death
VF = ventricular fibrillation

Clinical, laboratory, electrocardiographic, and electrophysiologic study. The following clinical data were collected: family history of SCD (<45 years of age) or BrS, documented atrial fibrillation (AF), documented VF, syncope, age at the first cardiac event, and implantation of implantable cardioverter-defibrillator (ICD).

A 12-lead ECG was recorded in all 93 BrS patients, and RR interval, PR interval (lead II), QRS duration (lead V_5), corrected QT interval (lead V_2), QRS axis, J-point amplitude (leads V_2), and amplitude of several points of ST-segment (leads V_1, V_2, V_3) were measured.

Signal-averaged ECG was recorded and analyzed in 91 patients by using a signal-averaged ECG system (1200EPX, Arrhythmia Research Technology, Milwaukee, Wisconsin). Three parameters were assessed using a computer algorithm: 1) total filtered QRS duration; 2) root mean square voltage of the terminal 40 ms of the filtered QRS complexes (V_{40}); and 3) duration of low-amplitude signals <40 μV of the filtered QRS complexes (T_{40}). Late potential was considered present when the 2 criteria (V_{40} <18 μV and T_{40} >38 ms) were fulfilled.

Electrophysiologic study (EPS) was performed in 79 BrS patients (21 documented VF patients, 30 syncope alone patients, and 28 asymptomatic patients). A maximum of 3 programmed ventricular extrastimuli were delivered from the right ventricular apex and RVOT, unless VF was induced. No patients received antiarrhythmic drugs before EPS. The atrio-His and His-ventricular intervals were measured during sinus rhythm. The EPS was conducted after all subjects gave written informed consent.

Genetic testing for the presence of an *SCN5A* mutation was also conducted.

Exercise testing. Treadmill exercise testing was conducted in all 93 patients with BrS and 102 control subjects. Neither BrS patients nor control subjects used antiarrhythmic agents. A symptom-limited or submaximal (up to 90% of the age-predicted maximum heart rate) graded treadmill exercise testing similar to modified Bruce protocol was used. All 93 BrS patients and 102 control subjects were in normal sinus rhythm, and none had atrioventricular block at the exercise testing. The standard 12-lead ECGs were recorded at rest, at the end of each exercise stage, at peak exercise, and at every minute during recovery. The amplitude of ST-segment from the isoelectric line at the right precordial leads (V_1 to V_3 leads) and QRS width at V_5 lead were manually measured. The ST-segment point was defined as the point

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where the vertical line from the end point of QRS at V_5 lead intersected the precordial leads. We also measured peak J-point amplitude in lead V_2 as a depolarization parameter, and amplitude of the point, which was 40 and 80 ms later than the peak J-points (ST40, ST80) in lead V_2 as a repolarization parameter. Measurements of ECG parameters were performed as the mean of 3 beats by single electrocardiologist who knew nothing about the patients. Significant augmentation of ST-segment elevation was defined as ST-segment amplitude increase ≥0.05 mV in at least 1 of V_1 to V_3 leads at early recovery (1 to 4 min at recovery) compared with the ST-segment amplitude at baseline (pre-exercise). We also recorded heart rate and blood pressure during exercise testing.

The HRR was defined as decay of heart rate from peak exercise to 1 min at recovery.

Follow-up. Follow-up was started after undergoing treadmill exercise testing. All patients with BrS were routinely followed up at the outpatient clinic of our hospital. The ICD implantation was performed in 63 BrS patients (20 documented VF patients, 25 syncope alone patients, and 18 asymptomatic patients). Antiarrhythmic drugs were prescribed for 7 patients; 2 patients who had episodes of VF but refused implantation of ICD (disopyramide 300 mg daily for 1 patient, and amiodarone 200 mg daily for another patient), 2 patients who had AF (quinidine 300 mg daily), and 3 patients who had previous history of both VF and AF and implanted ICD (quinidine 300 mg daily for 1 patient, amiodarone 200 mg daily for 2 patients).

Cardiac events were defined as SCD or aborted cardiac arrest, and VF or sustained ventricular tachyarrhythmia documented by ICD or ECG recordings.

Statistical analysis. Data were analyzed with Dr. SPSS II for Windows software package (SPSS Inc., Chicago, Illinois). Numeric values are expressed as mean ± SD. The chi-square test, Student *t* test, or 1-way analysis of variance was performed when appropriate to test for statistical differences. All p values <0.05 were considered statistically significant. Event rate curves were plotted according to the Kaplan-Meier method, and were analyzed with the log-rank test. Univariate and multivariate Cox regression were performed to assess whether 7 indexes can be significant and independent predictors of subsequent cardiac events. We used the forward step-wise approach with p to enter a value of 0.05 for multivariate analysis. Augmentation of ST-segment elevation at early recovery, family history of SCD or BrS, spontaneous coved-type ST-segment elevation, presence of *SCN5A* mutation, late potential, VF inducibility during EPS, and previous episodes of VF were included as indexes.

Results

There were no significant differences between 93 BrS patients and 102 control subjects with respect to age at exercise testing, sex, QRS duration (lead V_5), and QTc interval (lead V_2), as summarized in Table 1. The RR interval and PR interval (lead II) were significantly longer in BrS patients than in control subjects.

Table 1 Initial Characteristics of Patients and Control Subjects

	Brugada Patients (n = 93)	Control Subjects (n = 102)	p Value
Age at exercise testing, yrs	46 ± 14	46 ± 17	NS
Sex, male	91 (98%)	97 (95%)	NS
Electrocardiographic characteristics, ms			
RR	952 ± 151	903 ± 140	0.020
PR	178 ± 30	165 ± 24	0.001
QRS duration	98 ± 16	98 ± 20	NS
QTc	416 ± 44	406 ± 30	NS

Values are mean ± SD or n (%).
QTc = corrected QT interval.

Response of ST-segment elevation during treadmill exercise testing. Among 93 BrS patients, significant augmentation of ST-segment elevation mostly associated with coved pattern at early recovery phase was observed in 34 BrS patients (37% [group 1]), but not in the remaining 59 BrS patients (63% [group 2]). Conversely, ST-segment augmentation was never observed in any of the 102 control subjects (34 of 93 [37%] vs. 0 of 102 [0%], $p < 0.0001$). Typical responses of ST-segment amplitudes of 3 groups are shown in Figure 1. Composite data of serial changes of ST-segment amplitude in V_1 and V_2 leads during exercise testing are illustrated in Figure 2A. The serial changes of ST-segment amplitude in V_3 lead showed the same trend (not shown). In group 1, ST-segment amplitude decreased at peak exercise and started to reascend at early recovery, and culminated at 3 min of recovery (Figs. 1A and 2A). In contrast, ST-segment amplitude of group 2 patients and control subjects decreased at peak exercise, and gradually returned to the baseline amplitude rather than showing augmentation (Figs. 1B to 1D and 2A). Significant differences were identified between group 1 and group 2 patients in the ST-segment amplitude in leads V_1 and V_2 from peak exercise to 6 min of recovery, whereas no major differences were observed between group 2 patients and control subjects (Fig. 2A). Composite data of serial changes of peak J-point amplitude, ST40, and ST80 amplitudes are presented in Figure 2B. The peak J-point amplitude and ST40 amplitude during recovery showed the same trend as the ST-segment amplitude in Figure 2A. Significant differences were identified between group 1 and group 2 patients in the peak J-point and ST40 amplitudes from peak exercise to 6 min of recovery. The ST80 amplitude showed significant differences between group 1 and group 2 patients at 2, 3, and 4 min of recovery. At peak exercise, the peak J-point amplitude increased in 34 (37%) of 93 Brugada patients and in 26 (26%) of 102 control subjects, although the ST-segment

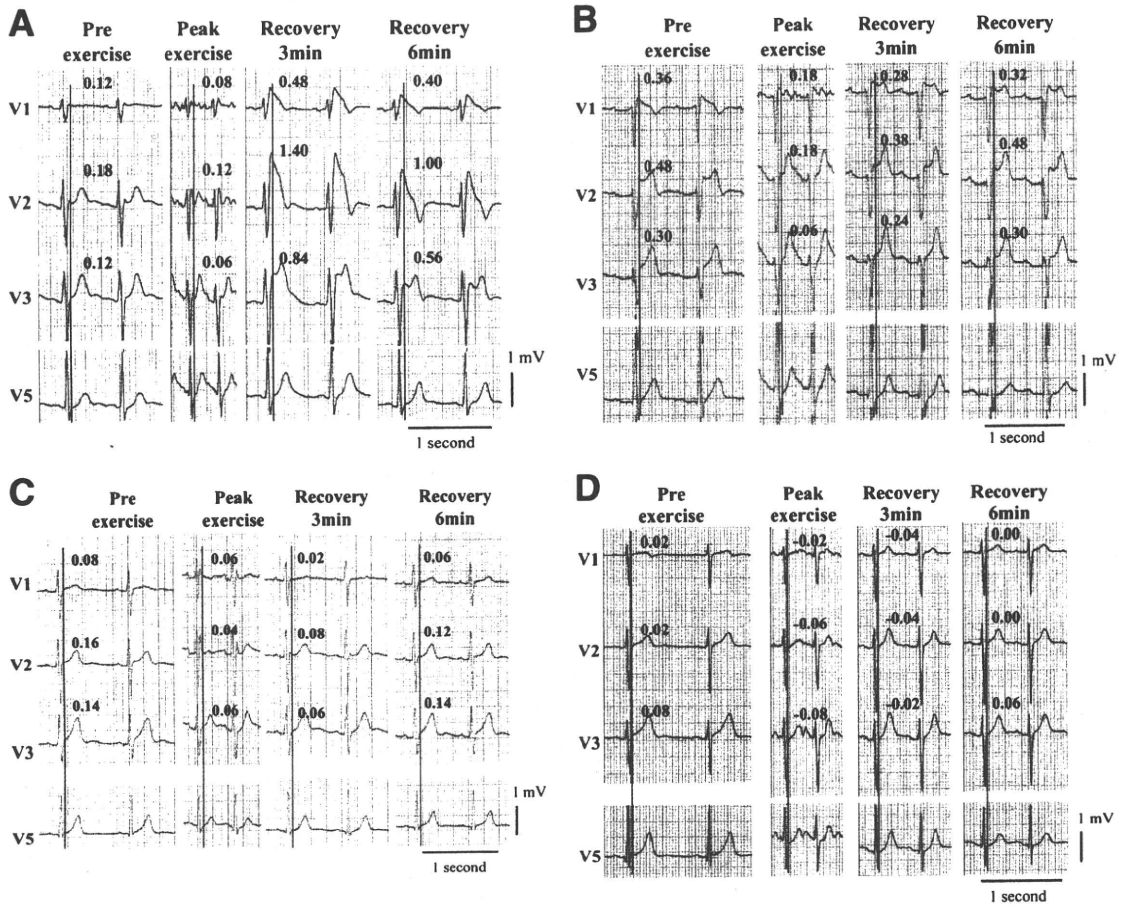

Figure 1 **Typical Responses of ST-Segment Amplitude in Leads V_1, V_2, V_3, and V_5 During Exercise Testing in Brugada Syndrome Patients**

(A) In the group 1 Brugada patient showing saddle-back type ST-segment (lead V_2) at baseline, ST-segment amplitude slightly decreased at peak exercise, but reascended at early recovery (3 min), resulting in typical coved-type ST-segment elevation. **(B, C)** In the group 2 Brugada patient and **(D)** in the control subject, ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline at recovery. It is noteworthy that the peak J-point amplitude in lead V_2 was augmented despite not showing ST-segment augmentation in **A** and **C**. The ST-segment amplitudes are shown as numeric values expressed in millivolts (mV). The **red vertical line** indicates the line from the end point of the QRS interval at electrocardiography lead V_5.

amplitude and ST40 amplitude decreased in most patients of both groups.

Comparison of HRR is shown in Figure 3. The HRR of group 1 patients was significantly larger than that of group 2 patients (32 ± 15 vs. 23 ± 10, p = 0.0007) and control subjects (32 ± 15 vs. 26 ± 10, p = 0.021). The differences of HRR between group 2 patients and control subjects were also statistically significant (23 ± 10 vs. 26 ± 10, p = 0.026).

Although there were no sustained or nonsustained ventricular arrhythmias throughout exercise testing, single premature ventricular complexes were observed during exercise in 8 of the group 1 patients and in 11 of the group 2 patients, and at recovery in 10 of the group 1 patients and in 9 of the group 2 patients. There were no significant differences between groups 1 and 2 in incidences of premature ventricular complexes.

Clinical, laboratory, electrocardiographic, and electrophysiologic characteristics. Comparison of the clinical, laboratory, electrocardiographic, and electrophysiologic characteristics between groups 1 and 2 patients are shown in Table 2. There were no significant differences in these characteristics between groups 1 and 2 except for the presence of *SCN5A* mutation and late potential (*SCN5A* mutation, 17% vs. 5%, p = 0.048; late potential, 82% vs. 53%, p = 0.004).

Follow-up. The mean follow-up period for the 93 BrS patients was 75.7 ± 38.4 months. During follow-up, 25 of all 93 BrS patients (27%) had cardiac events, and the incidence of cardiac events was significantly higher in group 1 than in group 2 patients (44% vs. 17%, p = 0.004). The period from exercise testing to cardiac events ranged from 1 to 78 months (median 12 months). One patient in group 2, who refused implantation of ICD and was taking disopyr-

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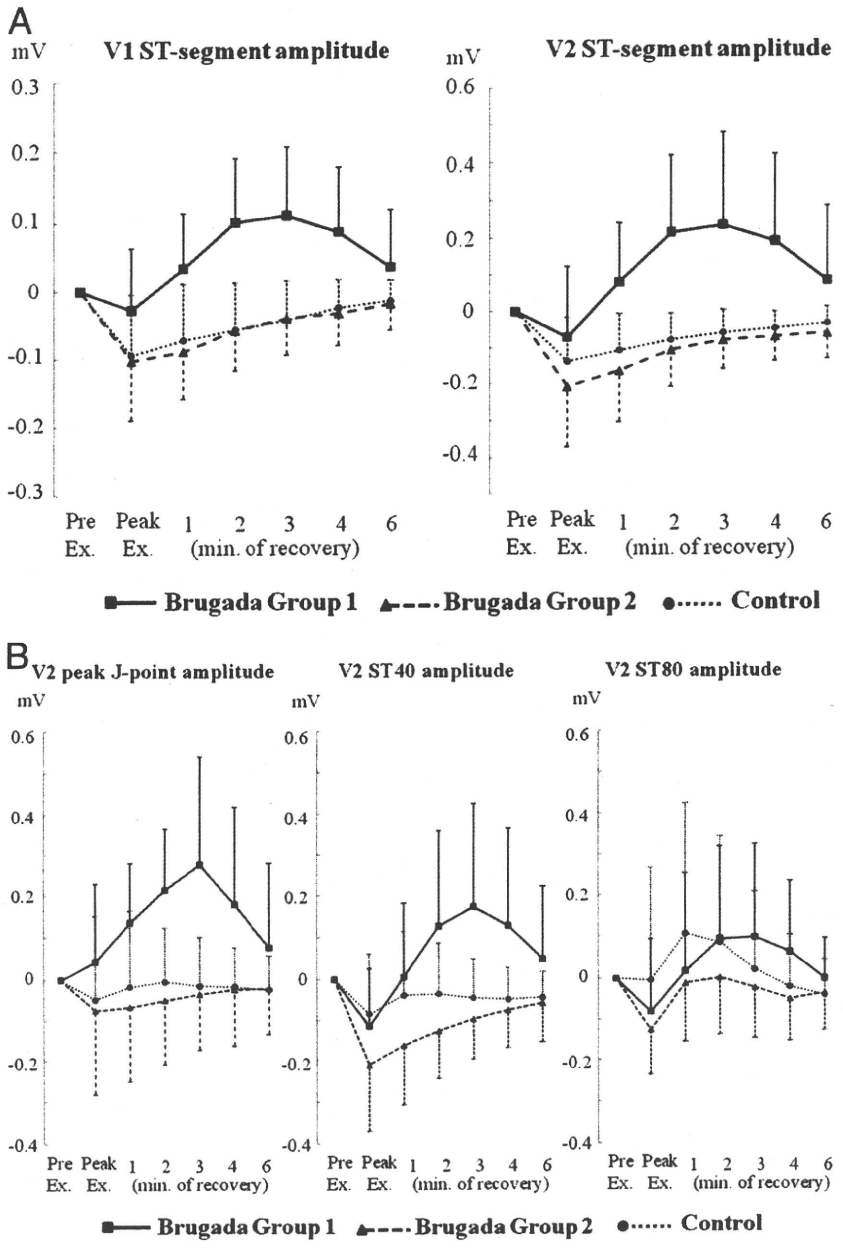

Figure 2 **Composite Data of Serial Changes of ST-Segment Amplitude**

(A) Composite data of serial changes of ST-segment amplitude in lead V_1 **(left)** and lead V_2 **(right)** during exercise (Ex.) testing in group 1 Brugada syndrome patients **(squares)** and group 2 Brugada syndrome patients **(triangles)**, and in control subjects **(circles)**. **(B)** Peak J-point amplitude **(left)**, ST40 amplitude **(middle)**, and ST80 amplitude **(right)** in lead V_2. The ST-segment amplitude decreased at peak exercise and started to reascend at early recovery, and culminated at 3 min of recovery in group 1 Brugada patients. In the group 2 Brugada patients and control subjects, the ST-segment amplitude decreased at peak exercise and gradually recovered to the baseline level during recovery. The peak J-point amplitude and ST40 amplitude during recovery showed the same trend as the ST-segment amplitude. Since ST80 amplitude was influenced by T wave, especially at rapid heart rate, the trends of the 3 groups were somewhat different from ST-segment amplitude or ST40 amplitude. The ST-segment amplitudes are shown as values compared to pre-exercise ST-segment amplitudes. $p < 0.05$.

amide 300 mg daily, died of VF. Three of 7 patients with medication had cardiac events, including 1 death.

Predictors of outcome. Kaplan-Meier analysis demonstrated significant differences in the time to the first cardiac event depending on the presence of ST-segment augmentation during recovery from exercise (Fig. 4A). Group 1 patients had a significantly higher cardiac event rate than group 2 patients (log-rank, $p = 0.0029$). Previous history of VF (Fig. 4B) and positive *SCN5A* mutation (Fig. 4C) also had significant values for occurrence of subsequent cardiac events ($p = 0.0013$ and $p = 0.028$, respectively); however, spontaneous coved-type ST-segment elevation did not predict cardiac events ($p =$