Identification of high-risk syncope related to ventricular fibrillation in patients with Brugada syndrome

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BACKGROUND Syncope in patients with Brugada syndrome is usually associated with ventricular tachyarrhythmia, but some episodes of syncope can be related to autonomic disorders.

OBJECTIVE The purpose of this study was to investigate the characteristics of syncope to differentiate high-risk syncope episodes from low-risk events in patients with Brugada syndrome.

METHODS We studied 84 patients with type 1 electrocardiogram and syncope. Patients were divided into 2 groups: patients with prodrome (prodromal group; n = 41) and patients without prodrome (nonprodromal group; n = 43).

RESULTS Ventricular fibrillation (VF) was documented at index event in 19 patients: 4 patients (21%) with documented VF experienced a prodrome prior to the onset of VF, whereas 15 patients (79%) did not have symptoms prior to documented VF ($P < .01$). Twenty-seven patients in the prodromal group and 7 patients in the nonprodromal group were considered to have syncope related to autonomic dysfunction. Syncope in other patients was defined as unexplained syncope. During the follow-up period (48 ± 48 months), recurrent syncope due to VF occurred in 13 patients among patients with only unexplained syncope and was more frequent in the nonprodromal group (n = 10) than in the prodromal group (n = 3; $P = .044$). In multivariate analysis, blurred vision (hazard ratio [HR] 0.20) and abnormal respiration (HR 2.18) and fragmented QRS (HR 2.39) were independently associated with the occurrence of VF.

CONCLUSION Syncope with prodrome, especially blurred vision, suggests a benign etiology of syncope in patients with Brugada syndrome.

KEYWORDS Brugada syndrome; Neurally mediated syncope; Prodrome; Syncope; Ventricular fibrillation

ABBREVIATIONS **BS** = Brugada syndrome; **ECG** = electrocardiogram; **f-QRS** = fragmented QRS; **HUT** = head-up tilt; **ICD** = implantable cardioverter-defibrillator; **NMS** = neurally mediated syncope; **OH** = orthostatic hypotension; **VF** = ventricular fibrillation

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Introduction

Syncopal episodes in patients with Brugada syndrome (BS) are usually associated with the occurrence of ventricular tachyarrhythmias. Spontaneous type 1 electrocardiogram (ECG) and episodes of syncope are predictors of sudden cardiac arrest in patients with BS.[1–4] However, patients with BS often have autonomic nerve disorders,[5,6] and some of their episodes of syncope can result from low-risk events (such as neurally mediated syncope [NMS] or orthostatic hypotension [OH]). In the general population, NMS has been shown to be one of the major causes of syncope.[7] Although syncopal episodes associated with autonomic disorders usually have prodromal symptoms and occur in specific situations, differentiation of low-risk episodes from high-risk syncopal episodes due to ventricular tachyarrhythmias is often difficult in patients with BS. Moreover, vagal nerve activation causes NMS as well as exaggeration of ST-segment elevation and induces ventricular fibrillation (VF) in patients with BS.[8] It is possible that vagal nerve activation initiates NMS-like symptoms and subsequently induces VF. Determination of the etiology of syncope episodes is important to identify patients with BS who are at risk of sudden cardiac arrest and who require an implantable cardioverter-defibrillator (ICD). When vagal nerve activation induces VF, prodrome accompanied by vagal nerve activation can appear immediately before the episodes. In the present study, we investigated the characteristics of syncope and determined high-risk syncope associated with ventricular arrhythmias to differentiate high-risk syncope episodes from low-risk events. We also determined whether

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patients have any prodrome before VF in association with vagal nerve activation.

Methods

We first enrolled 92 patients with a history of syncope and faintness who had BS-like ECGs. We excluded 7 patients because of inability to confirm type 1 ECG by the consensus report of BS[2] spontaneously or after a drug-provocation test. We also excluded 1 patient with a history of VF due to ischemic heart disease who had undergone coronary-artery bypass surgery for triple vessel disease. Therefore, this study group comprised 82 males and 2 females with BS (mean age 47 ± 12 years). All patients had episodes of syncope (76 patients) or faintness (8 patients) and had type 1 ECG (61 spontaneous and 23 pilsicainide-induced). We divided the patients into 2 groups according to syncope episodes associated with the existence of prodrome: patients with prodromal symptoms or specific situations (prodromal group; n = 41) and patients without any prodromal symptoms or specific situations (nonprodromal group; n = 43). We defined prodromal symptoms as blurred vision, diaphoresis, palpitations, chest discomfort, and symptoms associated with urination.

No patients were from the same family. Echocardiography and chest radiography were performed in all patients, and no abnormalities were found. We interviewed all patients at the time of history to obtain information on situations and characteristics of syncope. The follow-up duration was defined as the time between the first event and the final visit date. The mean follow-up duration of all patients was 48 ± 48 months. Syncope was classified on the basis of the European Society of Cardiology guidelines for the diagnosis and management of syncope (version 2009).[9] NMS was diagnosed by the combination of results of a head-up tilt (HUT) test[9] and situations and symptoms of syncopal episodes. Documentation of VF was defined as cardiopulmonary arrest at the hospital or in the ambulance. Detection of VF was defined as records of continuous ECG monitoring, automated external defibrillator, and ICD.

The HUT test[9] was performed in 35 patients (25 patients in the prodromal group and 10 patients in the nonprodromal group). The test was performed in the late afternoon in a fasting state. An intravenous line was inserted before the HUT test. Each patient lay on the tilt table in the supine position for 10 minutes at first. Then the tilt table was kept at an angle of 75° for 20 minutes. When the passive control test result was negative, the patient was returned to the supine position. Thereafter, low-dose isoproterenol infusion (≈0.01−0.03 μg/kg/min) was started to increase the heart rate. After an increase of more than 20% over baseline in the heart rate had been achieved, the tilt table was again kept at an angle of 75° for 25 minutes. A positive HUT test was defined as appearance of syncope or presyncope associated with reflex hypotension or bradycardia. The HUT response was classified as cardioinhibitory, vasodepressor, or mixed type on the basis of the predominancy of cardioinhibitory or vasodepressor reflex.

Standard 12-lead ECGs (0−150-Hz filter) and additional V_1-V_3 at the 3rd intercostal space were recorded simultaneously. We evaluated the RR, PQ, and QRS intervals in lead II as well as the QT interval, ST level at J point, and existence of fragmented QRS (f-QRS) in leads V_1-V_3 of the 12-lead ECG at the patients' first visit. We previously reported that type 0 ECG was defined as coved ST-segment elevation ≥ 2 mm with an absent or shallow negative T wave (depth ≤ 1 mm)[10] (Figure 1).

The presence of late potential was evaluated with a signal-averaged ECG (ART 1200EPX, noise level < 0.3 μV, and high-pass filtering of 40 Hz with a bidirectional 4-pole Butterworth). The filtered QRS duration, root-mean-square voltage of the terminal 40 ms in the filtered QRS complex, and duration of low-amplitude signals <40 μV in the terminal filtered QRS complex were measured by the signal-averaged ECG. Late potentials (LPs) were considered to be positive when the following 2 criteria were met: root-mean-square voltage of the terminal 40 ms in the filtered QRS complex < 20 μV and duration of low-amplitude signals <40 μV in the terminal filtered QRS complex > 38 ms.[11]

All the patients who underwent an electrophysiological study had received an explanation of the risks involved and had provided written informed consent. The electrophysiological study was performed in 72 patients. All those patients underwent coronary angiography, and none of the patients had significant coronary artery stenosis. Induction of ventricular arrhythmia was attempted by programmed electrical stimulation from the right ventricular apex, right ventricular outflow, and left ventricle, with a maximum of 3 extrastimuli at 2 cycles.[12,13] The criterion for the induction of ventricular arrhythmia was the induction of sustained polymorphic ventricular tachycardia or VF with double or less extrastimuli.

The genetic analysis of *SCN5A* was performed in 46 patients as previously described[14] in compliance with guidelines for human genome studies of the ethics committee of Okayama University.

Statistics

Continuous data were expressed as means ± standard deviation. Comparisons among means were performed with a 2-way analysis of variance coupled with Scheffe's test. A comparison of 2 groups was made with the Student *t* test for unpaired data (patients' data), as appropriate. Categorical data and percentage frequencies were analyzed by using a nonparametric test (Man-Whitney *U* test). The Fisher exact test was conducted for a comparison of proportions between the groups. Survival and event rates were determined by using the Kaplan-Meier method and compared between the groups with a 2-sample log-rank test. We compared clinical parameters and prognosis between the prodromal and nonprodromal groups, and then we used Cox proportional hazards model to detect risk factors of VF. To examine prognostic values from predictors of VF and determine cutoff values, an analysis of receiver-operating characteristic

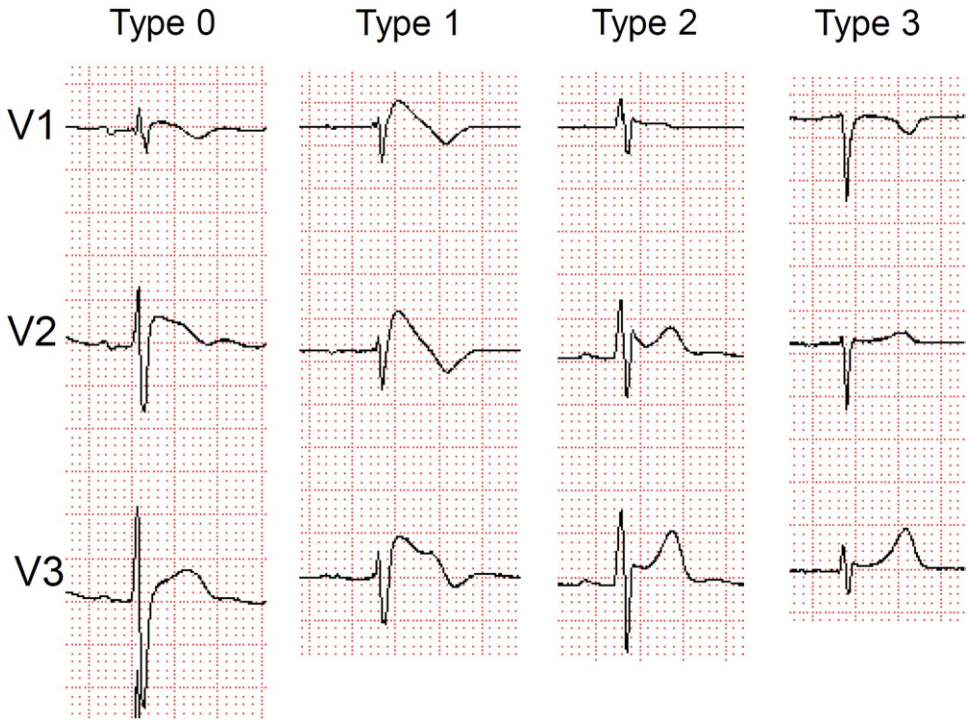

Figure 1 Types of ECGs in patients with Brugada syndrome. **A:** Type 0 is defined as ECG with coved ST-segment elevation ≥ 2 mm and a shallow negative T wave (≤1 mm) or having no negative T wave. **B–D:** Type 1−3 ECGs are defined according to the consensus reports of Brugada syndrome. ECG = electrocardiogram.

curves was done. Significance was defined as $P < .05$. JMP version 7.0 (SAS Institute, Inc, Cary, NC) was used for data analysis.

Results

Clinical characteristics and ECG parameters in the prodromal and nonprodromal groups

There was no difference in the baseline characteristics between the prodromal group and the nonprodromal group (Table 1). VF during the follow-up period in patients without VF documentation at their index hospitalization was more frequent in the nonprodromal group than in the prodromal group (Figure 2A). The percentage of patients in the nonprodromal group who received ICD implantation was higher than that in the prodromal group (Table 1). There were no differences in the inducibility of VF by programmed electrical stimulations, incidence of family history of sudden death, and frequency of *SCN5A* mutation between the prodromal group and the nonprodromal group. In ECG parameters, the nonprodromal group had a longer PQ interval in lead II and a longer QT interval in lead V_1 than those in the prodromal group. There were no differences in the indices of ECG types and f-QRS between the 2 groups. The filtered QRS interval in the signal-averaged ECG was longer in the nonprodromal group than in the prodromal group.

Features of syncope

Table 2 shows clinical characteristics of syncope. There were no differences in incidences of syncope and faintness between the 2 groups. Patients in the prodromal group experienced prodrome immediately before episodes of syncope or faintness: blurred vision was the most common prodrome, and about one-third of the patients experienced syncope in association with urination. Abnormal respiration was frequently observed in the nonprodromal group. There were no differences in the frequencies of convulsion, incontinence, and injury between the 2 groups.

Syncope often occurred in the supine position during sleep in patients in the nonprodromal group. Patients in the prodromal group often experienced syncope while they were standing, and this resulted in falling down after the episode. There were no differences in other syncope between the 2 groups. A positive HUT test result was observed more frequently in the prodromal group (54%) than in the nonprodromal group (10%, $P = .012$).

Table 3 shows the clinical characteristics of syncope in patients without VF detection at index hospitalization. When subjects were limited to patients who did not have VF at index hospitalization, blurred vision was the most common prodrome in the prodromal group. The clinical features of these patients' subgroups were similar to the data including patients who had VF at index hospitalization (Tables 2 and 3).

Causes of syncope

At the time of index hospitalization, VF was documented in 19 patients (4 in the prodromal group and 15 in the nonprodromal group) and was not documented in 65 patients (37 in the prodromal group and 28 in the nonprodromal group) (Table 2 and Figure 2A). One patient in the nonpro-

Table 1 Clinical and ECG parameters in patients with and without prodromal symptoms

Variables	Prodromal group	Nonprodromal group	*P*
Number of patients	41	43	
Clinical parameters			
Age (y)	46 ± 11	48 ± 13	NS
Female gender	1 (2%)	1 (2%)	NS
Family history	11 (27%)	10 (23%)	NS
SCN5A mutation	7/18 (39%)	13/28 (46%)	NS
Inducible VF/VT at PES	19/35 (54%)	19/37 (52%)	NS
Follow-up period (m)	44 ± 42	52 ± 52	NS
ICD implantation	14 (34%)	31 (72%)	.00036
ECG parameters			
ECG type			
Type 1	28 (68%)	33 (77%)	NS
Type 0	16 (39%)	16 (39%)	NS
RR II (ms)	963 ± 164	991 ± 183	NS
PQ II (ms)	170 ± 21	182 ± 27	.029
QRS II (ms)	111 ± 18	112 ± 20	NS
QT			
V_1 (ms)	385 ± 33	403 ± 39	.027
V_2 (ms)	400 ± 39	413 ± 38	NS
V_3 (ms)	393 ± 33	406 ± 38	NS
ST level			
V_1 (mV)	0.19 ± 0.10	0.26 ± 0.26	NS
V_2 (mV)	0.33 ± 0.16	0.41 ± 0.32	NS
V_3 (mV)	0.21 ± 0.09	0.25 ± 0.18	NS
Fragmented QRS			
Number of spikes			
V_1	2.7 ± 0.8	2.8 ± 1.0	NS
V_2	2.5 ± 1.3	3.0 ± 1.2	NS
V_3	2.0 ± 1.1	2.3 ± 1.0	NS
Total spikes	7.2 ± 2.6	8.1 ± 2.7	NS
Existence of f-QRS	14 (34%)	23 (50%)	NS
Signal averaged ECG			
Filtered QRS (ms)	119 ± 16	130 ± 21	.012
LAS40 (ms)	45 ± 14	49 ± 15	NS
RMS40 (μV)	15 ± 9	12 ± 9	NS
Late potential positive	27 (66%)	34 (79%)	NS

Values represent n (%) and mean ± standard deviation.

ECG = electrocardiogram; f-QRS = fragmented QRS; ICD = implantable cardioverter-defribillator; LAS40 = duration of low-amplitude signals <40 μV in the terminal filtered QRS complex; NS = nonsignificant; PES = programmed electrical stimulation; RMS40 = root-mean-square voltage of the terminal 40 ms in the filtered QRS complex; VF = ventricular fibrillation; VT = ventricular tachijcardia.

dromal group who had syncope episodes coincident with bradyarrhythmia was diagnosed as having sick sinus syndrome. Among 64 patients without documented VF at their index hospitalization, we considered causes of syncope to be NMS in 21 patients (all in the prodromal group) and OH in 13 patients (6 in the prodromal group and 7 in the nonprodromal group) on the basis of results of HUT tests and situations of the episodes, but we could not determine the cause of syncope in 30 patients (unexplained syncope: 10 in the prodromal group and 20 in the nonprodromal group). VF was documented at the time of recurrent syncope in 13 patients with unexplained syncope and was more frequent in the nonprodromal group (n = 10) than in the prodromal group (n = 3; P = .044) during the follow-up period (Figures 2A and 2B). One patient in the nonprodromal group was diagnosed with epilepsy during follow-up. None of the patients diagnosed with NMS or OH experienced VF during follow-up.

Predictors of VF

Table 4 shows results of univariate analysis for the prediction of VF in clinical and ECG parameters between patients with VF and patients without VF. In this table, documentation of VF includes both VF at index hospitalization and VF during the follow-up period. Clinical parameters were not different between patients with documented VF (VF group) and patients without documented VF (non-VF group). In ECG parameters, appearance of spontaneous type 1 or type 0 ECG, prolonged QT interval in leads V_1 and V_2, and existence of f-QRS were associated with the occurrence of VF (Table 4). Although prodrome was usually related to non-VF episodes, about 20% of the patients in the VF group experienced prodrome before the onset of VF (Table 5): prodromal symptoms before VF were blurred vision (rare), palpitations, and chest discomfort. VF often occurred at rest in the supine position and was accompanied by convulsion and abnormal respiration during the episode. Non-VF episodes usually occurred with prodrome (especially blurred vision and diaphoresis) while patients were standing or urinating.

Figures 2B and 2C show results of the Kaplan-Meier analysis of the new occurrence of VF in patients without documented VF at their index hospitalization. Absence of prodrome (especially blurred vision, relation to urination, and diaphoresis) was associated with the subsequent occurrence of VF episodes during the follow-up period (Figure 2C).

Table 6 shows results of univariate analysis for the prediction of VF in patients with BS. Prodromal symptoms (especially blurred vision) and syncope while standing were low-risk symptoms for the occurrence of VF, and syncope without prodrome was a predictor of VF occurrence during follow-up. Abnormal respiration and convulsion during the episode were related to the occurrence of VF. Appearance of type 0 or type 1 ECG and existence of late potential or f-QRS were also predictors of VF.

Multivariate analysis that included the variables listed in Table 6 indicated that syncope with blurred vision was a low-risk symptom for the occurrence of VF and that abnormal respiration and f-QRS were independent risk factors for the occurrence of VF. Receiver-operating characteristic curves for patients with VF showed that absence of blurred vision had high sensitivity (93.8%) but low specificity (50.0%), abnormal respiration had low sensitivity (43.8%) but high specificity (92.3%), and f-QRS had intermediate sensitivity (71.9%) and specificity (73.1%). Figure 2D shows that the receiver-operating characteristic curve was graphed by the combination of fQRS, abnormal respiration, and absence of blurred vision. This combination had an excellent accuracy of diagnosis for patients with VF (sensitivity of 84.4% and specificity of 82.7%).

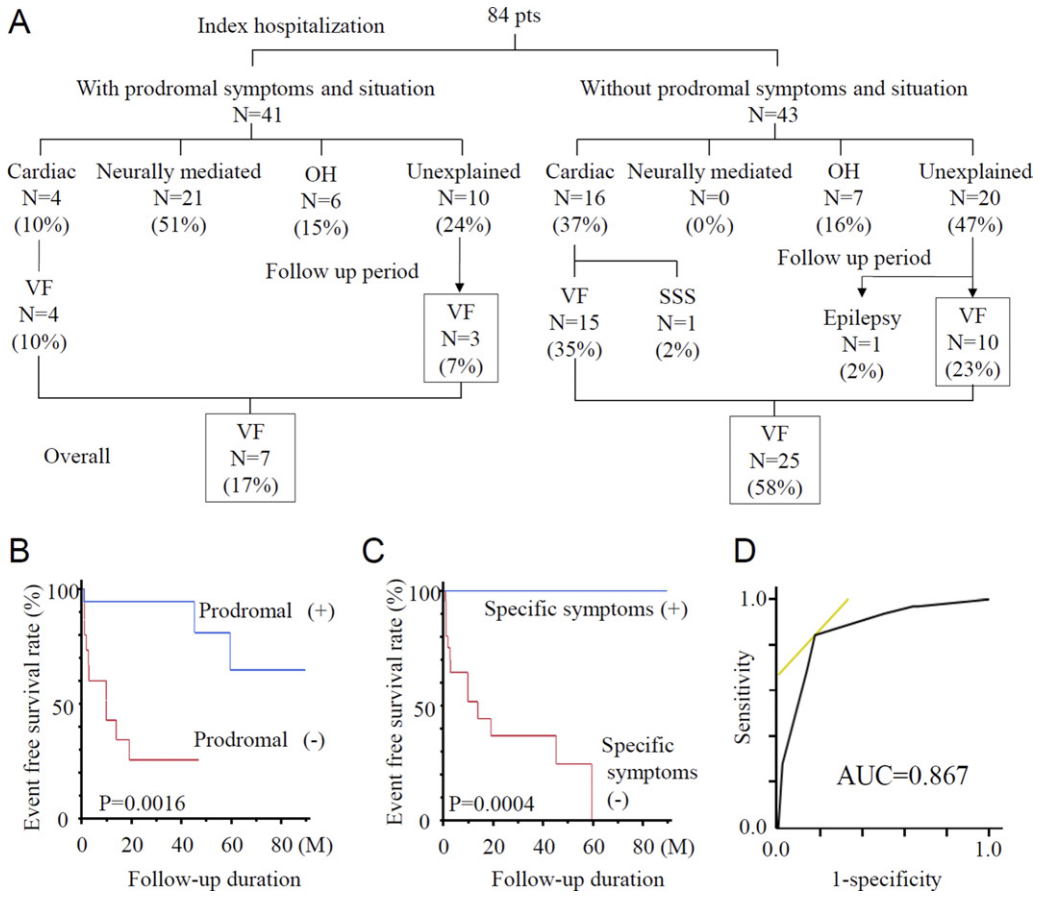

Figure 2 Prognosis and risk factors for the occurrence of VF in patients with Brugada syndrome. **A:** Causes of syncope in Brugada syndrome patients with and without prodromal syndrome and situations at the initial visit and during the follow-up period. **B:** Freedom from lethal arrhythmic events for patients with and without prodromal symptoms and specific situations (blurred vision, relation to urination, diaphoresis, palpitations, and chest discomfort). Patients in the nonprodromal group often experienced recurrence of syncope owing to VF within 2 years from the first visit. **C:** Freedom from events for patients with and without existence of specific symptoms (blurred vision, diaphoresis, and relation to urination). Patients with specific symptoms did not suffer from VF during the follow-up period. **D:** Receiver-operating characteristic curve of the combination of fQRS, abnormal respiration, and absence of blurred vision. This combination was the highest AUC and had excellent accuracy of diagnosis for patients having VF. AUC = area under the curve; f-QRS = fragmented QRS; OH = orthostatic hypotension; SSS = sick sinus syndrome; VF = ventricular fibrillation.

Discussion

New observations

We found that syncope without prodrome was a high-risk sign associated with VF episodes. Although blurred vision, relation to urination, and diaphoresis were not associated with the occurrence of VF, 2 other prodromal symptoms—palpitations and chest discomfort—might be associated with VF episodes. We also found that syncope associated with VF often occurred in the supine position during sleep and was accompanied by convulsion and abnormal respiration. Therefore, absence of prodrome (especially blurred vision) and existence of abnormal respiration and f-QRS were important risk factors for the occurrence of VF in patients with BS and syncope. When syncopal episodes without documented VF at index hospitalization were accompanied by absence of blurred vision and existence of abnormal respiration and fQRS, VF was more likely in follow-up. Although vagal nerve activation can induce VF in patients with BS, patients did not have any vagally induced prodrome before the onset of VF.

Syncope episodes in BS

Previous studies showed that spontaneous type 1 ECG and syncope episodes were predictors of arrhythmic events in patients with BS.[15,16] The FINGER study[17] showed that the cardiac event rate in patients with syncope was lower than that in patients with aborted sudden cardiac death but higher than that in asymptomatic patients. Thus, in previous studies, prognosis for patients with syncope was better than for patients with documented VF, although the syncope could have resulted from VF. This might be due to the fact that syncope episodes include both high-risk episodes related to VF and low-risk benign syncope episodes such as NMS and OH. Yokokawa et al[5] reported that one-third of the patients with BS had NMS, and they concluded that an impaired balance of the autonomic nervous system was related to their syncopal episodes. NMS[6] was also observed in asymptomatic patients with Brugada-type ECG. Thus, an indication for ICD implantation requires confirmation of the mechanism of syncope in patients with BS being benign or not. The HUT test is a useful tool for augmenting vagal

Table 2 Characteristics of syncope in patients with and without prodromal symptoms

Variables	Prodromal group	Nonprodromal group	*P*
Number of patients	41	43	
Symptom			
Syncope	38 (93%)	38 (88%)	NS
Faintness	3 (7%)	5 (12%)	NS
Prodromes			
Blurred vision	28 (68%)	0 (0%)	<.0001
Relation to urination	11 (27%)	0 (0%)	.00018
Diaphoresis	10 (24%)	0 (0%)	.00042
Palpitation	9 (22%)	0 (0%)	.0009
Chest discomfort	6 (15%)	0 (0%)	.0088
Patients' condition after onset of syncope			
Convulsion	6 (15%)	10 (23%)	NS
Incontinence	4 (10%)	7 (16%)	NS
Falling down	15 (37%)	8 (19%)	NS
Any injury	3 (7%)	2 (5%)	NS
Abnormal respiration	3 (7%)	15 (35%)	.0018
Position at the onset of syncope			
Supine	3 (7%)	18 (42%)	.0002
Sitting	15 (37%)	12 (28%)	NS
Standing	23 (56%)	13 (30%)	.016
Situation at the onset of syncope			
On exertion	1 (2%)	1 (2%)	NS
Standing-up	7 (17%)	7 (16%)	NS
Bathing	4 (10%)	2 (5%)	NS
Rest	7 (17%)	19 (44%)	.0068
Sleeping	3 (7%)	15 (35%)	.0018
Drinking	4 (10%)	6 (14%)	NS
Initial diagnosis of the syncope			
Arrhythmias			
VF	4 (10%)	15 (35%)	.0055
SSS	0 (0%)	1 (2%)	NS
Neurally mediated syncope	21 (51%)	0 (0%)	<.001
Orthostatic hypotension	6 (15%)	7 (16%)	NS
Unexplained	10 (24%)	20 (47%)	.035

Values represent n (%).

NS = nonsignificant; SSS = sick sinus syndrome; VF = ventricular fibrillation.

nerve activity and inducing NMS, but positive results of a HUT test in BS patients with syncope might incorrectly indicate syncope associated with VF as being benign vagal syncope.

Another dilemma related to autonomic nerve activation in BS is that vagal nerve stimulation could aggravate the pathophysiology of BS. Vagal nerve activation mediated by acetylcholine caused abbreviated epicardial action potential and augmented ST-segment elevation in ECGs in an experimental model of BS.[18] Heterogeneous loss of the phase 2 dome of the action potential initiates phase 2 reentry and polymorphic ventricular tachycardia. Infusion of acetylcholine into the coronary artery augmented ST-segment elevation without coronary vasospasm and induced VF.[8,19] Physiological conditions enhanced vagal nerve activity and also augmented ST-segment elevation in right precordial leads in relation to the occurrence of VF.[20]

Although prodrome was often accompanied by benign syncope[9,21] (such as NMS and OH), arrhythmic syncope had less prodromal symptoms.[22,23] It is difficult to differentiate benign syncope from ventricular tachyarrhythmia in patients with BS because vagal nerve activation can induce NMS as well as VF.[8,19] In the present study, we showed that patients did not have any vagally induced prodrome before the onset of VF. We analyzed prodrome and situations in detail and consequently found that syncope with blurred vision, diaphoresis, or a situation related to urination indicated benign symptoms mediated by NMS or OH in patients with BS. Palpitations and chest discomfort could be prodrome at the onset of VF.

Table 3 Characteristics of syncope in patients without VF detection at index hospitalization between the prodromal group and the nonprodromal group

Variables	Prodromal group	Nonprodromal group	*P*
Number of patients	37	28	
Symptom			
Syncope	34 (92%)	23 (82%)	NS
Faintness	3 (8%)	5 (18%)	NS
Prodromes			
Blurred vision	26 (70%)	0 (0%)	<.0001
Relation to urination	11 (30%)	0 (0%)	.0060
Diaphoresis	10 (27%)	0 (0%)	.0099
Palpitation	7 (19%)	0 (0%)	.038
Chest discomfort	4 (11%)	0 (0%)	NS
Patients' condition after onset of syncope			
Convulsion	4 (11%)	6 (21%)	NS
Incontinence	4 (11%)	6 (21%)	NS
Falling down	14 (38%)	4 (14%)	.0256
Any injury	3 (8%)	2 (7%)	NS
Abnormal respiration	3 (8%)	6 (21%)	NS
Position at the onset of syncope			
Supine	2 (5%)	13 (46%)	.0002
Sitting	5 (18%)	12 (32%)	NS
Standing	23 (62%)	10 (36%)	NS
Situation at the onset of syncope			
On exertion	1 (3%)	1 (4%)	NS
Standing-up	7 (19%)	7 (25%)	NS
Bathing	3 (8%)	1 (4%)	NS
Rest	5 (14%)	15 (54%)	.0001
Sleeping	2 (5%)	11 (39%)	.0007
Drinking	3 (8%)	4 (14%)	NS
Initial diagnosis of the syncope			
Arrhythmias			
VF	0 (0%)	0 (0%)	–
SSS	0 (0%)	1 (4%)	NS
Neurally mediated syncope	21 (57%)	0 (0%)	<.0001
Orthostatic hypotension	6 (16%)	7 (25%)	NS
Unexplained	10 (27%)	20 (71%)	.014

Values represent n (%).

NS = nonsignificant; SSS = sick sinus syndrome; VF = ventricular fibrillation.

Table 4 Clinical and ECG parameters in patients with and without VF

Variables	VF	Non-VF	*P*
Number of patients	32	52	
Clinical parameters			
Age (y)	49 ± 11	47 ± 13	NS
Female gender	1 (3%)	1 (2%)	NS
Family history	9 (28%)	12 (23%)	NS
SCN5A mutation	12/24 (50%)	8/22 (36%)	NS
Inducible VF/VT at PES	16/30 (53%)	21/42 (50%)	NS
Follow-up period (m)	68 ± 55	36 ± 38	.0024
ICD implantation	29 (91%)	16 (31%)	<.0001
ECG parameters			
ECG type			
Type 1	29 (91%)	32 (62%)	.0032
Type 0	19 (59%)	13 (25%)	.0014
RR II (ms)	991 ± 145	970 ± 189	NS
PQ II (ms)	177 ± 32	176 ± 20	NS
QRS II (ms)	115 ± 22	109 ± 17	NS
QT			
V_1 (ms)	410 ± 36	384 ± 35	.0018
V_2 (ms)	422 ± 37	397 ± 37	.0055
V_3 (ms)	404 ± 38	397 ± 34	NS
ST level			
V_1 (mV)	0.24 ± 0.15	0.22 ± 0.22	NS
V_2 (mV)	0.35 ± 0.22	0.38 ± 0.28	NS
V_3 (mV)	0.21 ± 0.12	0.24 ± 0.15	NS
Fragmented QRS			
Number of spikes			
V_1	3.0 ± 0.9	2.6 ± 0.9	NS
V_2	3.4 ± 1.2	2.4 ± 1.2	.0005
V_3	2.4 ± 1.1	2.0 ± 1.1	NS
Total spikes	8.8 ± 2.4	6.9 ± 2.6	.0014
Existence of f-QRS	23 (72%)	14 (27%)	<.0001
Signal averaged ECG			
Filtered QRS (ms)	132 ± 19	121 ± 18	.0099
LAS40 (ms)	53 ± 16	44 ± 13	.014
RMS40 (μV)	11 ± 9	15 ± 8	.020
Late potential positive	27 (84%)	34 (65%)	NS

Values represent n (%) and mean ± standard deviation.

ECG = electrocardiogram; f-QRS = fragmented QRS; ICD = implantable cardioverter-defibrillator; LAS40 = duration of low-amplitude signals <40 μV in the terminal filtered QRS complex; NS = nonsignificant; PES = programmed electrical stimulation; RMS40 = root-mean-square voltage of the terminal 40 ms in the filtered QRS complex; VF = ventricular fibrillation; VT = ventricular tachijcardia.

Generally, symptoms with prodrome resulted from benign syncope in relation to autonomic dysfunction and were not associated with the occurrence of VF in patients with BS. Although the present study showed that the clinical course of syncope episodes with prodrome was benign, we should emphasize that the existence of NMS and OH in patients with BS cannot predict whether patients will have new onset of VF in the future.

Limitations

We selected patients with type 1 ECG and a history of syncope. Their causes of syncope were classified as documented VF, NMS, OH, and unexplained syncope. However, unexplained syncopal episodes could include different forms between low-risk events (ie, NMS and OH) and high-risk events (ie, VF). The FINGER study[17] indicated that symptomatic patients more frequently underwent ICD implantation than did asymptomatic patients. The second consensus report[2] showed that confounding factors affecting ECG abnormality or syncope should be carefully excluded. Although this report described different factors of ECG abnormality in detail, the clinical features of various types of syncope episodes were not described. In this study, the unexplained syncope group would be patients of high risk for VF and they underwent ICD implantation prophylactically. As a result, they had an appropriate discharge of ICD and sudden cardiac death was prevented.

The results of the HUT test were more frequently positive in the prodromal group than in the nonprodromal group. However, we could not perform the HUT test in all patients with VF, especially in patients in whom VF or aborted cardiac arrest was documented at index hospitalization. Therefore, the number of patients who took a HUT test was limited and a positive HUT test result was not a significant predictor of VF. Although there were no patients with a positive HUT test result in the VF group, it could not be concluded in this study that a tilt test confirms benign syncope in patients with Brugada-type ECG.

Table 5 Characteristics of syncope in patients with and without VF

Variables	VF	Non-VF	*P*
Number of patients	32	52	
Syncope			
Prodromes			
If any	7 (22%)	35 (67%)	<.0001
Blurred vision	2 (6%)	26 (50%)	<.0001
Relation to urination	0 (0%)	11 (21%)	.0049
Diaphoresis	0 (0%)	11 (21%)	.0049
Palpitation	4 (13%)	5 (10%)	NS
Chest discomfort	4 (13%)	2 (4%)	NS
Patients' condition after onset of syncope			
Convulsion	13 (41%)	3 (6%)	<.0001
Incontinence	6 (19%)	5 (10%)	NS
Falling down	7 (22%)	16 (30%)	NS
Any injury	0 (0%)	5 (9%)	NS
Abnormal respiration	14 (44%)	4 (8%)	<.0001
Position at the onset of syncope			
Supine	14 (43%)	7 (13%)	.0016
Sitting	13 (41%)	14 (27%)	NS
Standing	5 (16%)	31 (60%)	<.0001
Situation at the onset of syncope			
On exertion	2 (6%)	0 (0%)	NS
Standing-up	0 (0%)	14 (27%)	.0011
Bathing	2 (6%)	4 (8%)	NS
Rest	15 (47%)	11 (21%)	.013
Sleeping	13 (41%)	5 (10%)	.0006
Drinking	4 (13%)	6 (12%)	NS

Values represent n (%).

NS = nonsignificant; VF = ventricular fibrillation.

Table 6 Univariate and multivariate analyses in all patients

	Univariate			Multivariate		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Prodomes						
If any	0.24	0.09–0.57	.0008	–		
Blurred vision	0.11	0.02–0.37	<.0001	0.20	0.03–0.75	.0145
Abnormal respiration	3.26	1.55–6.81	.0023	2.18	1.02–4.64	.045
Convulsion	2.40	1.15–4.86	.021	–		
Syncope while standing	0.37	0.13–0.89	.025	–		
Type 1 ECG	3.86	1.37–16.1	.0078	–		
Type 0 ECG	2.57	1.27–5.34	.0083	–		
Late potential positive	2.85	1.19–8.44	.018	–		
Existence of f-QRS	3.57	1.70–8.19	.0006	2.39	1.11–5.62	.0261

CI = confidence interval; ECG = electrocardiogram; f-QRS = fragmented QRS; HR = hazard ratio.

Conclusion

Syncope episodes with prodromal symptoms and specific situations, especially blurred vision, are benign symptoms in patients with BS. Absence of prodrome is a high-risk sign of the occurrence of VF in BS patients with syncope episodes.

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