


ORIGINAL RESEARCH

# Significance of Exercise-Related Ventricular Arrhythmias in Patients With Brugada Syndrome

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**BACKGROUND:** Sinus tachycardia during exercise attenuates ST-segment elevation in patients with Brugada syndrome, whereas ST-segment augmentation after an exercise test is a high-risk sign. Some patients have premature ventricular contractions (PVCs) related to exercise, but the significance of exercise-related PVCs in patients with Brugada syndrome is still unknown. The objective of this study was to determine the significance of exercise-related PVCs for predicting occurrence of ventricular fibrillation (VF) in patients with Brugada syndrome.

**METHODS AND RESULTS:** The subjects were 307 patients with Brugada syndrome who performed a treadmill exercise test. We evaluated the occurrence of PVCs at rest, during exercise and at the peak of exercise, and during recovery after exercise (0–5 minutes). We followed the patients for  $92 \pm 68$  months and evaluated the occurrence of VF. PVCs occurred in 82 patients (27%) at the time of treadmill exercise test: PVCs appeared at rest in 14 patients (4%), during exercise in 60 patients (20%), immediately after exercise (0–1.5 minutes) in 28 patients (9%), early after exercise (1.5–3 minutes) in 18 patients (6%), and late after exercise (3–5 minutes) in 12 patients (4%). Thirty patients experienced VF during follow-up. Multivariable analysis including symptoms, spontaneous type 1 ECG, and PVCs in the early recovery phase showed that these factors were independently associated with VF events during follow-up.

**CONCLUSIONS:** PVCs early after an exercise test are associated with future occurrence of VF events. Rebound of vagal nerve activity at the early recovery phase would promote ST-segment augmentation and PVCs in high-risk patients with Brugada syndrome.

**Key Words:** Brugada syndrome ■ exercise test ■ premature ventricular contractions ■ sudden death ■ ventricular fibrillation

Ventricular fibrillation (VF) frequently occurs at night in association with parasympathetic nerve activation during sleep in patients with Brugada syndrome.<sup>1,2</sup> Occurrence of VF is rare during exercise<sup>2</sup> since the activated sympathetic nerve suppresses arrhythmogenesis in patients with Brugada syndrome. Sinus tachycardia during exercise usually reduces ST-segment elevation in right precordial leads,<sup>3</sup> but some patients have augmentation of ST-segment elevation in the early recovery phase after an exercise

test.<sup>4</sup> ST-segment augmentation after an exercise test can predict lethal arrhythmic events during follow-up. ST-segment augmentation can be caused by withdrawal of sympathetic nerve activation and rebound of parasympathetic nerve activity after exercise.<sup>5</sup> A rise in body temperature during exercise is also a possible cause of augmentation of ST-segment elevation.<sup>6</sup>

Although occurrence of VF during exercise is rare in patients with Brugada syndrome, ventricular tachyarrhythmias as well as supraventricular arrhythmias

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## CLINICAL PERSPECTIVE

### What Is New?

- The significance of exercise test–induced premature ventricular contractions has not been recognized in patients with Brugada syndrome.
- Patients with premature ventricular contractions during early recovery phase after an exercise test frequently experienced ventricular fibrillation during follow-up.

### What Are the Clinical Implications?

- Premature ventricular contractions during the early recovery phase (1.5–3 minutes) after an exercise test by vagal rebound can identify the high-risk patients with Brugada syndrome.
- Exercise tests are safe because they do not induce ventricular fibrillation in patients with Brugada syndrome.
- Exercise tests can be a useful risk stratification tool for predicting future occurrence of ventricular fibrillation in patients with Brugada syndrome.

## Nonstandard Abbreviation and Acronym

**TMT** treadmill exercise test

sometimes occur in association with exercise<sup>4,7–9,10</sup>. Moreover, monomorphic ventricular tachycardia (VT) can occur in some patients with Brugada syndrome during exercise.<sup>11–13</sup> Detection of ventricular arrhythmias can be a high-risk sign in Brugada syndrome<sup>14,15</sup>; however, little is known about the significance of arrhythmias, especially ventricular tachyarrhythmias, associated with exercise.

The objective of this study was to clarify the incidence and significance of exercise-related arrhythmias, especially ventricular tachyarrhythmias, in patients with Brugada syndrome.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

### Subjects of the Study

The subjects of this study comprised 307 patients with Brugada-type ECG who visited our hospital. The mean age of the patients was 45±12 years (range, 17–79 years)

and men were predominant (299 men; 97%). At the first visit to the hospital, 219 patients were asymptomatic, 75 had syncope, and 13 had experienced aborted cardiac arrest. The diagnosis of Brugada syndrome was made according to the criteria of J-Wave-Syndromes Expert Consensus Statements.<sup>16</sup> Spontaneous type 1 was defined as the appearance of coved-type ST-segment elevation (J point  $\geq 0.2$  mV) without a sodium channel blocker. There were no patients from the same family. We followed all of the patients at our outpatient clinic.

This study was approved by the Ethics Committee on Human Research and Epidemiology of Okayama University, and analysis of the *SCN5A* gene was performed in 117 patients, in compliance with guidelines for human genome studies of the Ethics Committee of Okayama University.

### ECG Evaluations

All of the 307 patients performed a treadmill exercise test (TMT). All ECGs were recorded without the use of any cardiac drugs. We explained the methods, requirements, and risks of the exercise test and obtained informed consent before the TMT. A repeat exercise test was performed in 140 patients at  $\geq 1$  month after the first exercise test. The protocol of the exercise test was the Bruce protocol with symptom-limited or submaximal exercise (up to 90% of maximum predicted heart rate by age). A 12-lead ECG with leads V1 and V2 located at the third intercostal spaces was recorded at rest, at every stage during exercise, at peak exercise, and every 1 minute during the recovery phase to 5 minutes and 20 seconds after exercise with a low-pass filter of 0 to 25 Hz. We evaluated heart rate, blood pressure, ST-segment levels as the J point in leads V1 and V2, and occurrence of arrhythmias in each ECG recording phase. ST-segment elevation was measured as the calculated mean of 3 successive beats. ST-segment augmentation after exercise was defined as ST-segment amplitude increase  $\geq 0.05$  mV in one of leads V1 and V2 in the early recovery phase of the exercise test (2 and 3 minutes after peak exercise).<sup>4</sup> To classify the morphologies of the exercise-related premature ventricular contractions (PVCs), we defined morphologies of PVCs as superior axis ( $0^\circ$  to  $-90^\circ$  and  $+180^\circ$  to  $+270^\circ$ ) and inferior axis ( $0^\circ$  to  $+180^\circ$ ) in limb leads and right bundle-branch block (RBBB) type (voltage of R wave  $\geq$  voltage of S wave in lead V1) and left bundle-branch block (LBBB) type (voltage of R wave  $<$  voltage of S wave in lead V1). ECG patterns were reviewed blindly by 3 cardiologists (HM, TK, and SA).

### Statistical Analysis

Continuous data are expressed as means±SD values. Fisher's exact test or the  $\chi^2$  test was used for categorical

variables. Comparison of 2 groups was made with the Student *t* test or a nonparametric test for paired and unpaired data, as appropriate. Arrhythmic events were defined as occurrence of VT/VF, aborted cardiac arrest, sudden death, or appropriate therapy of an implantable cardioverter defibrillator (ICD). Time from the initial hospital visit to the first arrhythmic event during follow-up was analyzed with Cox's proportional hazards model. Hazard ratios and CIs are presented for results of univariable analysis. For multivariable analysis, we selected significant parameters (symptoms [history of syncope or VF], spontaneous type 1 ECG and exercise-related PVCs at the first exercise test) to assess predictors of VF events during follow-up. Survival curves were plotted by the Kaplan–Meier method and analyzed by the log-rank test. We also assessed the results of univariable analysis of exercise-related PVCs in all exercise tests including repeated exercise tests to determine the relation between PVCs and all VF events and to calculate the odds ratios (ORs). Significance was defined as  $P < 0.05$ . All statistical analyses were performed with the use of JMP version 14.2 (SAS Institute, Inc., Cary, NC). All authors had full access to and take full responsibility for the integrity of the data.

## RESULTS

### Characteristics of Patients and TMT

Table 1 shows the baseline characteristics of the patients. Spontaneous type 1 ECG appeared in 219 patients (71%). Fifty patients had a family history of sudden death before 45 years of age. *SCN5A* mutation was found in 14 of the 117 patients in whom genetic tests were performed.

The median of maximum exercise was stage 4 (minimum, stage 1; maximum, stage 7). Heart rate

increased until the peak of exercise and gradually decreased after the exercise test (Figure 1A). Systolic blood pressure rose during exercise and became highest at the peak of the exercise and during the early recovery phase from exercise, and then it gradually decreased during the late recovery phase (Figure 1B). Diastolic blood pressure increased slightly at the peak of exercise.

ST-segment level at the J point in leads V1 and V2 decreased during exercise and became minimum at the peak of exercise, and then it gradually recovered to the baseline level after exercise (Figure 1C). Augmentation of ST-segment elevation in leads V1 and V2 appeared during the recovery phase after exercise in 66 patients (Figure S1A through S1C). Patients who had ST-segment augmentation after exercise had higher ST-segment level at baseline and throughout the exercise test than did patients without ST-segment augmentation after exercise (Figure S1C). Horizontal ST-segment depression ( $\leq 0.1$  mV) in inferolateral leads was observed in 10 patients, and coronary artery disease was found in 1 of those patients (Figure S2). After percutaneous coronary stenting to the right and left descending branches of the coronary arteries, that patient still had spontaneous type 1 ECG but did not have ST-segment depression after an exercise test. None of the other 9 patients with ST-segment depression after exercise had ischemic heart disease or ventricular hypertrophy, and we considered that ECG change was false positive for ischemia.

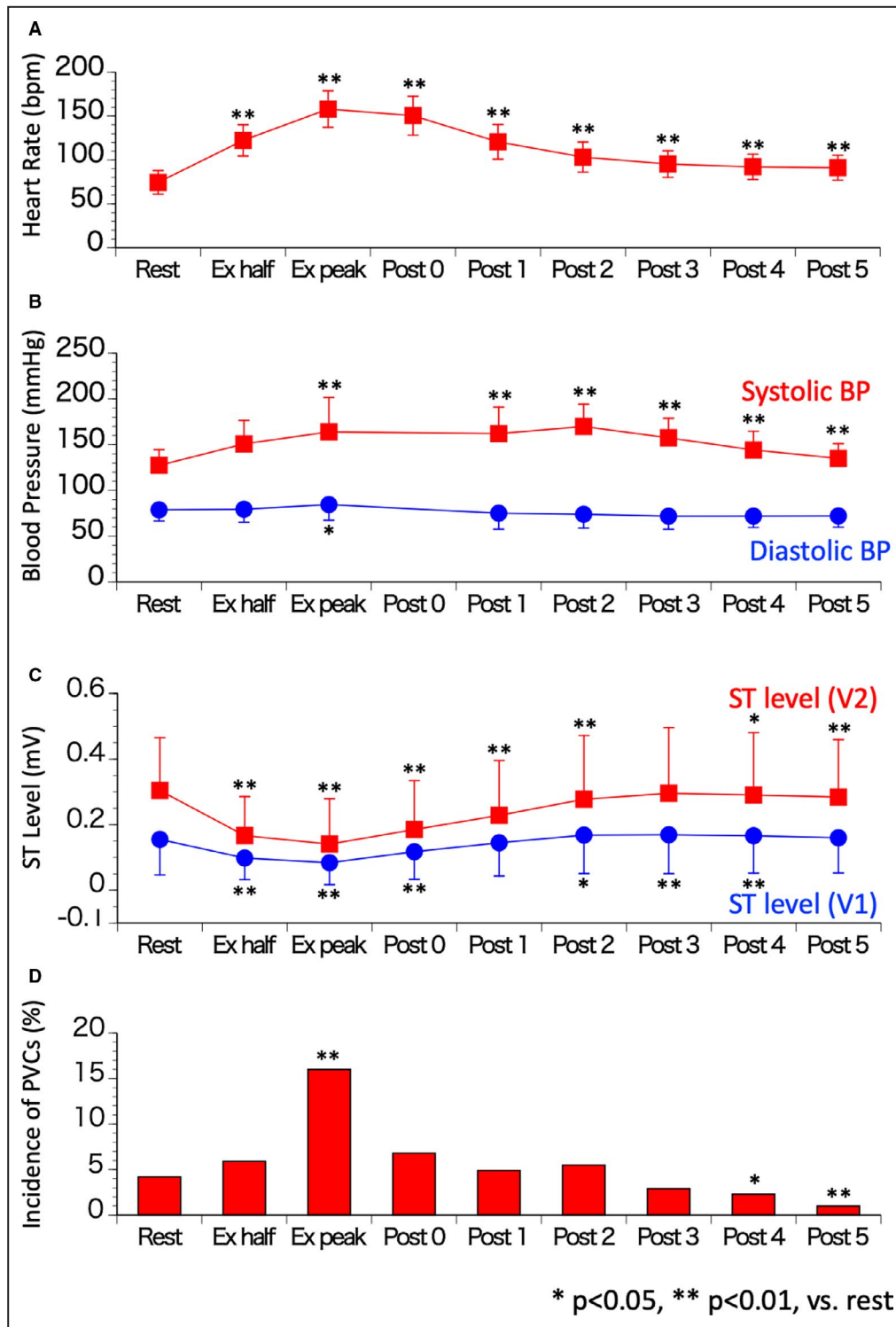
We implanted an ICD in 70 patients (28 asymptomatic patients, 29 patients with syncope, and 13 patients with VF). Thirty patients experienced lethal arrhythmic events during  $92 \pm 68$  months' follow-up (event ratio, 1.3%/year; asymptomatic patients,  $n=7$ ; patients with syncope,  $n=12$ ; patients with VF,  $n=11$ ). The arrhythmic events were appropriate ICD therapies in 21 patients,

**Table 1. Baseline Characteristics of Patients**

		Overall	Event+	Event–	<i>P</i> Value*
Total	Patients (%)	307	30	277	
Age	y	45±12	44±12	45±12	0.4668
Male	Patients (%)	299 (97.4%)	29 (96.7%)	270 (97.5%)	0.5651
FH of SD <45 y	Patients (%)	50 (16.3%)	5 (16.7%)	45 (16.2%)	1.0000
<i>SCN5A</i> mutation	Patients (%)	14/117 (12.0%)	4/25 (16.0%)	10/92 (10.9%)	0.4944
Spontaneous type 1	Patients (%)	219 (71.3%)	27 (90.0%)	192 (69.3%)	0.0182
Symptom at the first visit					
Asymptomatic	Patients (%)	219 (71.3%)	7 (23.3%)	212 (76.5%)	<0.0001
Symptomatic	Patients (%)	88 (28.7%)	23 (76.7%)	65 (30.7%)	
Syncope	Patients (%)	75 (24.4%)	12 (40.0%)	63 (22.7%)	
VF	Patients (%)	13 (4.2%)	11 (36.7%)	2 (7.2%)	
Event	Patients (%)	30 (9.8%)	30 (100.0%)	0 (0%)	...

FH indicates family history; SD, sudden death; and VF, ventricular fibrillation.

\*Comparison of patients with events and without events.



**Figure 1.** Changes in heart rate, blood pressure, ST level and incidence of PVC in association with exercise.

**A,** Heart rate. Heart rate increased after starting exercise and gradually recovered during the recovery phase. **B,** Blood pressure. Systolic blood pressure increased during and early after exercise and recovered to baseline during the late recovery phase. **C,** ST-segment level. ST-segment level decreased during exercise and then gradually recovered to baseline level after exercise. **D,** Incidence of premature ventricular contractions (PVCs). PVCs significantly increased at the peak of exercise. PVCs decreased during the late recovery phase compared with those at rest. \* $P < 0.05$ , \*\* $P < 0.01$ , vs rest. BP indicates blood pressure; and Ex, exercise test.

VT/VF in 8 patients, and sudden death in 1 patient. Patients who experienced VF events during follow-up more frequently had spontaneous type 1 ECG and were already symptomatic (Table 1). Other clinical factors, including age, sex, family history, and *SCN5A* mutation, were not different between patients with and those without VF events. There were no differences in occurrence of ST-segment augmentation or depression after exercise between patients with and without VF.

### Exercise-Related Ventricular Arrhythmias at the Time of the First TMT

Exercise-related PVCs were observed in 82 patients (26.7%) in the first TMT. PVCs appeared before exercise in 14 patients and during or after exercise in 81 patients (26.4%). PVCs occurred during exercise in 60 patients and in the recovery phase in 44 patients. PVCs occurred during or after exercise in 13 patients with PVCs before exercise. Twenty-three patients had PVCs during both the exercise and the recovery phase. PVCs significantly increased at the peak of exercise ( $n=48$ ) and immediately recovered to baseline after exercise (Figure 1D, Table 2). The frequency of PVCs was significantly reduced at 4 minutes (7 patients;  $P=0.0346$ ) and 5 minutes (3 patients;  $P=0.0043$ ) of the recovery phase compared with that before exercise (14 patients).

PVCs at 2 minutes of the recovery phase (2.0–3.0 minutes) occurred more frequently in patients with ST-segment augmentation than in patients without ST-segment augmentation (PVCs at 2 minutes of recovery: 7/66 patients with ST augmentation [10.6%], versus 10/241 patients without ST-segment augmentation [4.1%];  $P=0.0425$ ; Figure S1D). PVCs did not occur in association with ST-segment depression.

Patients with VF events more frequently had exercise-related PVCs, especially PVCs during 1.0–2.0 minutes and 2.0–3.0 minutes of the recovery phase, than did patients without VF events (Figure 2, Table 2). Furthermore, the frequencies of PVCs in the first half of 1 minute of the recovery phase (1.0–1.5 minutes) were not different between the 2 groups ( $P=0.2689$ ), but PVCs in the second half of 1 minute of the recovery phase (1.5–2.0 minutes) appeared more frequently in patients with VF events ( $P=0.0291$ ). Patients with VF events more frequently had PVCs in the first half and second half of 2 minutes of the recovery phase than did patients without VF events ( $P=0.0290$  and  $P=0.0051$ , respectively). Thus, the frequency of PVCs during 1.5 to 3.0 minutes of the recovery phase was significantly higher in patients with VF events than in patients without VF events (Table 2).

Various morphologies of PVCs were observed, and 24 patients had multifocal PVCs (Figure 3, Table 3).

**Table 2. Occurrences of Arrhythmias in Association With Exercise Test**

	Overall	Event+	Event–	P Value*
	307	30	277	
PVC (first TMT), n	82 (26.7)	13 (43.3)	69 (24.9)	0.0305
Rest	14 (4.2)	1 (3.3)	13 (4.7)	0.7349
During exercise	18 (5.9)	1 (3.3)	17 (6.1)	0.5353
Peak exercise	8 (15.6)	6 (20.0)	42 (15.2)	0.4890
Post 0 min	21 (6.8)	4 (13.3)	17 (6.1)	0.1387
Post 1 min	15 (4.9)	4 (13.3)	11 (4.0)	0.0241
Post 2 min	17 (5.5)	5 (16.7)	12 (4.3)	0.0051
Post 3 min	9 (2.9)	0 (0)	9 (3.3)	0.1371
Post 4 min	7 (2.3)	0 (0)	7 (3.6)	0.3792
Post 5 min	3 (1.0)	0 (0)	3 (1.1)	0.5674
Post 0–1.5 min	28 (9.1)	5 (16.7)	23 (8.3)	0.1313
Post 1.5–3 min	18 (5.9)	6 (20.0)	12 (4.3)	0.0005
Post (1.5–3 min)–(4–5 min)	14 (4.6)	6 (20.0)	8 (2.9)	<0.0001
PVCs $\geq$ cpl	12 (3.9)	2 (6.7)	10 (3.6)	0.4127
PAC, n (%)	52 (16.9)	3 (10.0)	49 (17.7)	0.2869
PAT/PSVT, n (%)	4 (1.3)	0 (0)	4 (1.4)	0.5083
PAF, n (%)	0 (0)	0 (0)	0 (0)	1.0000
SSS, n (%)	1 (0.3)	0 (0)	1 (0.4)	0.7421
Paroxysmal AVB, n (%)	1 (0.3)	0 (0)	1 (0.4)	0.7421
Complete RBBB, n (%)	1 (0.3)	0 (0)	1 (0.4)	0.7421
ST-segment depression, n (%)	8 (2.6)	1 (3.3)	7 (2.5)	0.7926
ST-segment augmentation, n (%)	66 (21.5)	5 (16.7)	61 (22.0)	0.4984

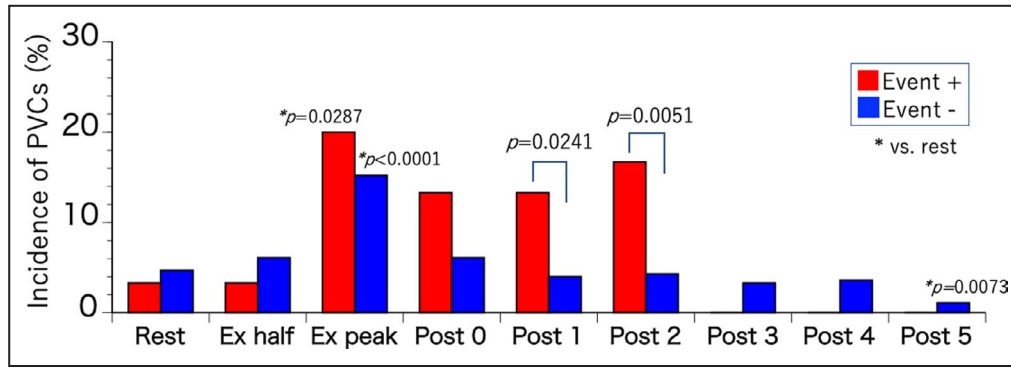
AVB indicates atrioventricular block; cpl, couplet; PAC, premature atrial contraction; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; RBBB, right bundle-branch block; and TMT, treadmill exercise test.

\*Comparison of patients with events and without events.

Eleven patients had couplet of PVCs ( $n=9$ ) or triplet of PVCs ( $n=2$ ) (Figure 3E), but exercise did not induce VT/VF. Couplet or triplet of PVCs and morphology of PVCs were not different between patients with and without VF during follow-up. PVCs with LBBB morphology, suggesting RV origin, frequently appeared during 1.5 to 3.0 minutes of the recovery phase (LBBB type,  $n=16$ ; RBBB type,  $n=6$ ;  $P<0.001$ ).

### Risk Factors Predicting VF Events During Follow-Up

Univariable analysis of baseline clinical characteristics showed that existence of spontaneous type 1 ECG and symptoms were associated with VF events during follow-up (Table 4, Figure 4A and 4B). Age, sex, family history, and *SCN5A* mutation were not associated with VF events. Among ECG changes and arrhythmias associated with exercise, occurrence of PVCs during 2.0 to

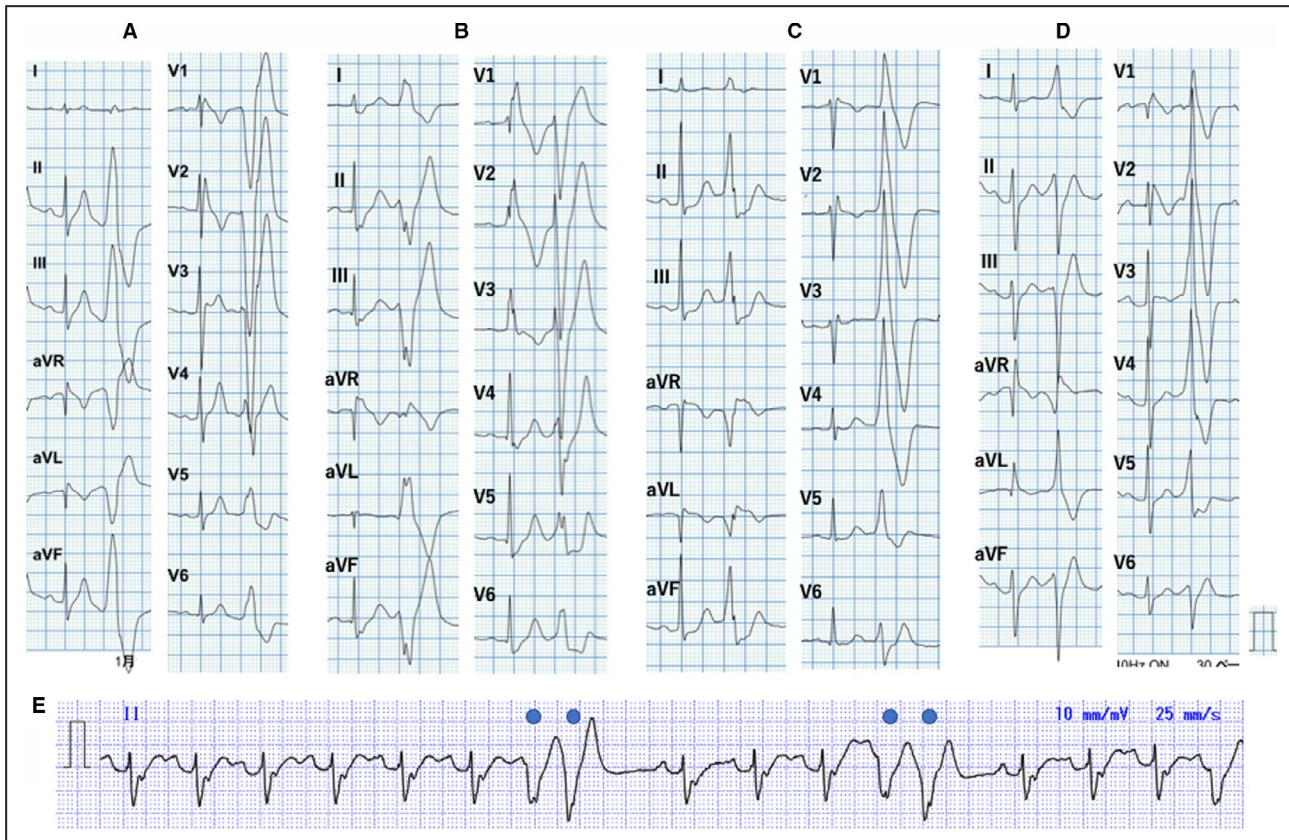


**Figure 2. Occurrence of premature ventricular contractions (PVCs) associated with exercise in patients with and those without VF events during follow-up.**

PVCs significantly increased at the peak of exercise in both patients with and those without VF events during follow-up. The frequencies of PVCs at 1 and 2 minutes of the recovery phase were significantly higher in patients with VF events than in patients without VF events. PVCs did not appear after 3 minutes of the recovery phase in patients with VF events. Ex indicates exercise test.

3.0 minutes of the recovery phase was associated with VF events. Occurrence of PVCs during the early recovery phase (1.5–3.0 minutes) showed a better correlation with VF events (Figure 4C). Sensitivity, specificity, and positive and negative predictive values of PVCs during the early recovery phase for occurrence of VF events were

20%, 96%, 33%, and 83%, respectively. Patients with VF events did not have PVCs after 4 minutes of the late recovery phase, and thus patients who had PVCs in the early recovery phase but did not have PVCs in the late recovery phase were at high risk for VF events during follow-up (Figure 4D). Morphology of PVCs and multifocal



**Figure 3. Morphologies of exercise-related premature ventricular contractions (PVCs).**

**A**, A PVC with left bundle-branch (LBBB) type and inferior axis (n=44). **B**, A PVC with LBBB and superior axis (n=33). **C**, A PVC with right bundle-branch block (RBBB) and inferior axis (n=9). **D**, A PVC with RBBB and superior axis (n=40). **E**, Occurrence of couplets of PVCs during the recovery phase (circles).

**Table 3. Morphologies of PVCs Associated With Initial and Repeat Exercise Test**

PVC Morphology	PVC at Initial TMT		PVC at Repeat TMT	
	Overall	Recovery 1.5–3 min	Overall	Recovery 1.5–3.5 min
LBBB type	60	16	75	23
LBBB+inferior axis	36	9	44	15
LBBB+superior axis	34	9	43	12
RBBB type	33	6	45	9
RBBB+inferior axis	8	0	9	1
RBBB+superior axis	28	6	40	9
Multifocal	11	4	14	6

LBBB indicates left bundle-branch block; PVC, premature ventricular contraction; RBBB, right bundle-branch block; and TMT, treadmill exercise test.

PVCs were not associated with VF events. Multivariable analysis including symptoms, spontaneous type 1 ECG, and PVCs in the early recovery phase (1.5–3.0 minutes) showed that these factors were independently associated with VF events (Table 5).

### Impact of PVCs in Repeat Exercise Tests on Overall VF Events

Repeat exercise tests were performed in 140 patients (2–15 times, average 2.9 times). Repeat exercise test added exercise-related PVCs in 24 additional patients out of 116 patients who did not have PVCs at the first exercise test (Table S1). The morphologies of PVCs were LBBB in 75 patients and RBBB in 45 patients (Table 3). Thirty-three patients who experienced VF previously or during follow-up (overall VF events) more frequently had exercise-related PVCs around 2 minutes of the recovery phase than did patients who never experienced VF at the end of follow-up (OR of PVCs during 2.0–3.0 minutes of exercise, 3.84; CI, 1.37–10.71;  $P=0.0102$ ; Figure S3). Exercise-related PVCs including those in repeat exercise tests showed that the PVCs during 1.5 to 3.5 minutes of the recovery phase were associated with overall VF episodes (OR of PVCs during 1.5–3.5 minutes of the recovery phase, 3.61; CI, 1.39–9.40;  $P=0.0084$ ). Patients who experienced VF did not have PVCs after 4 minutes of the recovery phase. Thus, excluding patients with PVCs after 4 minutes of the recovery phase from patients with PVCs during 1.5 to 3.5 minutes of the recovery phase was strongly associated with overall VF episodes (OR, 5.41; CI, 1.98–14.74;  $P=0.0010$ ) (Table S2).

### Exercise-Related Supraventricular Arrhythmias and Bradyarrhythmias

Supraventricular arrhythmias occurred in association with the first exercise test in 52 patients (52 patients with premature atrial complexes and 4 patients with paroxysmal atrial tachycardia or supraventricular tachycardia). Exercise revealed sinus node dysfunction, paroxysmal atrioventricular block, and transient

complete RBBB were observed in 1 patient each (Table 2).

Repeat TMT induced premature atrial contractions in 18 additional patients. New occurrence of supraventricular tachycardia and atrial fibrillation during repeat exercise tests were observed in 1 and 2 additional patients, respectively. Sick sinus syndrome and RBBB during repeat TMT tests were observed in 2 and 1 additional patients, respectively.

Supraventricular arrhythmias, bradyarrhythmias, and exercise-related ECG changes, such as ST changes, were not associated with VF events (Table 4, Table S1).

## DISCUSSION

### New Observations

Exercise-induced PVCs were observed in 26% of the patients with Brugada syndrome. In most of the patients, PVCs increased at the peak of exercise, then gradually decreased after exercise. However, in patients at high risk for VF, occurrence of PVCs showed a bimodal increment in association with the exercise test: PVCs increased at the peak of exercise and around 2 minutes of the recovery phase. Occurrence of PVCs in the early recovery phase (1.5–3.0 minutes) was associated with VF events during follow-up. Exercise test should be a part of routine examination for risk stratification in patients with Brugada syndrome.

### Exercise Test and Brugada Syndrome

Occurrence of lethal arrhythmias during exercise is very rare in patients with Brugada syndrome since catecholamine release attributable to acute sympathetic activation and parasympathetic withdrawal by exercise attenuate ST-segment elevation and inhibit the occurrence of VF.<sup>17,18</sup> Thus, there is no strict limitation on competitive sports even in symptomatic patients with Brugada syndrome.<sup>19</sup> Although an exercise test

**Table 4. Risk for VF of Baseline Characteristics and Exercise-Related Arrhythmias—Univariable Analysis**

	Hazard Risk	CI	P Value
Age	0.98	0.96–1.02	0.4085
Male	0.75	0.17–13.31	0.7842
FH of SD <45 y	1.03	0.35–2.49	0.9448
SCN5A mutation	1.52	0.44–3.99	0.4671
Spontaneous type 1	3.54	1.25–14.83	0.0144
Symptom at first visit			
Asymptomatic	1	...	...
Symptomatic	9.36	4.23–23.63	<0.0001
Syncope	5.36	2.16–14.42	0.0003
VF	55.24	21.3–153.4	<0.0001
PVC at the first TMT	2.03	0.97–4.17	0.0603
Rest	0.65	0.04–3.03	0.6488
During exercise	0.48	0.03–2.23	0.4111
Peak exercise	1.31	0.49–3.01	0.5619
Post 0 min	1.89	0.56–4.86	0.2744
Post 1 min	3.23	0.95–8.30	0.0586
Post 2 min	3.34	1.13–8.02	0.0320
Post 3 min	<0.01	1.81–1.81	0.1423
Post 4 min	<0.01	2.34–2.34	0.1961
Post 5 min	<0.01	4.95–4.95	0.3707
Post 0–1.5 min	1.90	0.64–4.57	0.2234
Post 1.5–3 min	4.02	1.49–9.21	0.0085
Post (1.5–3 min)–(4–5 min)	5.60	2.07–12.86	0.0016
PVC ≥ cpl	1.59	0.26–5.3	0.5513
PAC	0.86	0.32–1.96	0.7305
PAT/PSVT	<0.01	3.7–3.7	0.3022
PAF	<0.01	8.16–8.16	0.4861
SVT (PAT/PSVT/AF)	<0.01	2.51–2.51	0.2119
SSS	<0.01	7.83–0.83	0.4768
Paroxysmal AVB	<0.01	20.7–20.71	0.6611
Complete RBBB	<0.01	8.16–8.16	0.4861
ST depression	0.93	0.05–4.33	0.9398
ST augmentation	0.72	0.25–1.75	0.5031

AF indicates atrial fibrillation; AVB, atrioventricular block; cpl, couplet; FH, family history; PAC, premature atrial contraction; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; RBBB, right bundle-branch block; SD, sudden death; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; TMT, treadmill exercise test; VF, ventricular fibrillation.

is a safe examination for patients with Brugada syndrome, various ECG changes in an exercise test have been reported<sup>8,10,20,21</sup>: ST-segment augmentation at the early recovery phase,<sup>4,20</sup> QRS widening,<sup>3</sup> delayed heart rate recovery,<sup>21</sup> and arrhythmias. Some of these ECG changes are associated with VF. Makimoto et al<sup>4</sup> reported that augmentation of ST-segment elevation

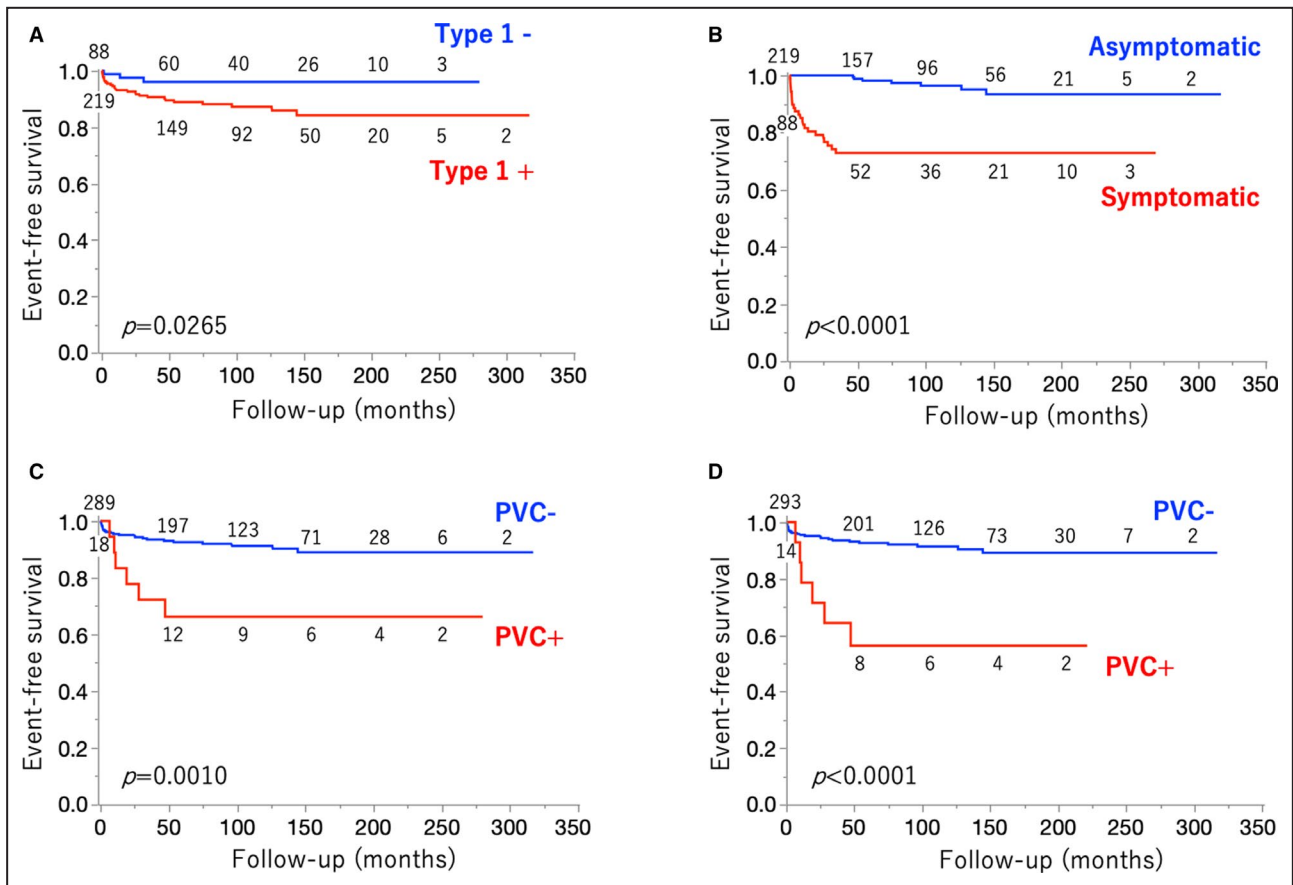
was observed in 37% of patients with Brugada syndrome in the early recovery phase after the exercise. ST-segment augmentation after exercise was associated with VF events during follow-up in both symptomatic and asymptomatic patients. During the recovery phase after exercise, the occurrences of sympathetic withdrawal and parasympathetic rebound and rise in body temperature can cause augmentation of ST-segment elevation.<sup>5,22</sup>

Some studies have also shown that arrhythmias can occur in association with exercise, but the significance of these arrhythmias has not been evaluated. Description of the occurrence of supraventricular arrhythmias associated with exercise test is very limited: One study showed the occurrence of premature atrial contractions in one patient and atrial fibrillation in 1 of 46 patients with Brugada syndrome.<sup>10</sup> The occurrence of ventricular tachyarrhythmias during an exercise test is also rare. Previous studies showed that monomorphic VT occurred during an exercise test,<sup>9,11–13,21</sup> but there have been no reports of VF induction during an exercise test. However, PVCs during or after an exercise test do not seem to be rare. The incidences of PVCs associated with exercise in patients with Brugada syndrome have been reported to be 0% to 33%,<sup>4,7,10,23</sup> but the impact of PVCs during exercise on the pathogenesis of Brugada syndrome has not been reported.

The present study showed that PVCs increased at the peak of exercise in overall patients. These PVCs at the peak of exercise were not associated with cardiac events, and PVCs at that phase might therefore not be directly associated with arrhythmogenicity in Brugada syndrome. PVCs significantly increased in the early recovery phase of exercise (1.5–3.0 minutes) in patients with VF during follow-up compared with those in patients without VF. Although the occurrence of PVCs in that phase was not frequent, PVCs occurring in only about 20% of the patients with future VF events, these PVCs might be directly associated with arrhythmogenicity in Brugada syndrome. Since ECG type and ST-segment level fluctuate in association with occurrence of VF<sup>24,25</sup> and arrhythmogenic substrate will progress in some patients,<sup>26</sup> occurrence of exercise-related PVCs could show day-by-day variation. Then repeat exercise test should be important to detect PVCs for risk stratification. The predominance of LBBB-type PVCs in this phase, usually indicating right ventricular origin, is compatible with the observation that the arrhythmogenic substrate of Brugada syndrome exists in the right ventricle.<sup>27</sup> Analysis of PVC morphologies might indicate a critical area in which ventricular arrhythmias are initiated in patients with Brugada syndrome.

The occurrence of PVCs in the recovery phase corresponded to the occurrence of ST-segment level augmentation after exercise. The mechanism of PVCs in this phase might coincide with the





**Figure 4. Event-free survival according to the clinical markers and premature ventricular contractions (PVCs) after exercise.** **A**, Prognosis of patients with and those without spontaneous type 1 ECG. Patients with spontaneous type 1 ECG had a shorter time to experience ventricular fibrillation (VF) events during follow-up than did patients without spontaneous type 1 ECG. **B**, Prognosis according to symptoms. Symptomatic patients had a worse prognosis than did asymptomatic patients. **C**, Prognosis according to occurrence of PVCs during 1.5 to 3 minutes of the recovery phase after the exercise test. Patients with PVCs more frequently had VF events than did patients without PVCs. **D**, Prognosis according to occurrences of PVCs during 1.5–3 minutes and after 4 minutes of the recovery phase. Patients who had PVCs during early recovery phase (1.5–3 minutes of the recovery) but did not have PVCs during the late recovery phase (after 4 minutes of the exercise) had a significantly shorter time to experience VF events during follow-up. Numbers along with the survival curves show number of patients at risk. HR indicates hazard ratio for occurrence of VF events by univariable analysis; and PVC, premature ventricular contractions during the early recovery phase.

mechanism of ST-segment augmentation: withdrawal of sympathetic activation and parasympathetic rebound. Interestingly, patients with cardiac events did not have PVCs after 4 minutes of the recovery phase. Recovery of heart rate and attenuation of ST-segment augmentation were also observed

at this phase, and it should indicate withdrawal of parasympathetic rebound after exercise. PVCs in the late recovery phase might not indicate arrhythmogenicity of Brugada syndrome. Thus, excluding patients with PVCs during the late recovery phase (after 4 minutes) from patients with PVCs during the early recovery phase (1.5–3.0 minutes) had strong association with VF events. Although PVCs in the early recovery phase might represent arrhythmogenicity in Brugada syndrome, there was no occurrence of VF related to exercise. Catecholamine release and sinus tachycardia during and after exercise prevented VF under the condition of parasympathetic rebound. Usually,  $\beta$ -blockers can reduce exercise-induced PVCs. PVCs associated with VF events are caused by vagal activation and sympathetic withdrawal after exercise, and effectiveness of  $\beta$ -blockers is not expected.

**Table 5. Risk for VF of Baseline Characteristics and Exercise-Related Arrhythmias—Multivariable Analysis**

	Hazard Risk	CI	P Value
Symptomatic (syncope and VF)	12.24	5.46–31.18	<0.0001
Spontaneous type 1 ECG	4.69	1.62–19.89	0.0028
PVCs 1.5–3 min after exercise	4.45	1.60–10.68	0.0062

PVC indicates premature ventricular contraction; and VF, ventricular fibrillation.

The present study showed that PVCs after exercise were associated with VF events in patients with Brugada syndrome, but the observations of this study do not forbid participation in sports activity. All exercise tests were accomplished safely and did not induce lethal arrhythmias. However, if patients have syncope related to exercise or monomorphic VT, sports participation should be avoided.

### Incidence of Exercise-Related PVCs

In the present study, we evaluated the response to exercise in patients with Brugada syndrome but not in control subjects. Previous studies showed that exercise-related PVCs occurred in 0% to 53%<sup>28</sup> of subjects who performed exercise tests, but some studies included patients with heart diseases<sup>29,30</sup> such as myocardial infarction. Data for healthy subjects are limited, and the incidence of PVCs induced by exercise in the general population has been reported to be 14% to 21%.<sup>28</sup> The definition of exercise-induced PVCs was different in each study, and comparison of the data in the present study with data in previous studies is not appropriate. It has been reported that VF events were most frequent in patients with previous VF events and that the frequency of VF events was the lowest in asymptomatic patients without spontaneous type 1 ECG.<sup>31</sup> Therefore, asymptomatic patients without spontaneous type 1 ECG only have little arrhythmogenic substrate and their characteristics might be close to normal subjects. When asymptomatic patients without spontaneous type 1 ECG were regarded as controls, the frequency of PVCs during the early recovery phase was significantly higher in patients with VF events than in controls (Figure S4). Thus, PVC at the early recovery phase from the exercise would be significantly more frequent in patients with VF events than in a general population.

### Limitation

This is a retrospective observational study, and we did not divide the patients to the derivation and validation cohorts. The number of events was not enough to divide the patient group. Moreover, occurrence of VF was rare in asymptomatic patients, and long follow-up periods should be required to confirm the prognosis of patients.

We measured ST-segment levels for ECG markers during exercise test. We also have reported that fragmented QRS, that is, multiple spikes within the QRS complex, is associated with VF events.<sup>32</sup> The fragmented QRS should be evaluated with 100 to 150 Hz of low-pass ECG filter, but exercise ECGs are usually recorded with 25 Hz of low-pass filter. Lowering of the low-pass filter can mask high-frequency spikes of fragmented QRS, and we could not evaluate fragmented QRS during exercise tests.

Nonsustained VF during sleeping will not cause any symptoms, but an ICD will detect it and cardioversion can be performed. Then, the detection of end points in patients with an ICD could be higher than that in patients without an ICD. However, some studies showed that VF was not detected by an insertable loop recorder even in symptomatic patients,<sup>33</sup> and nonsustained VF might be rare in patients with Brugada syndrome.

This study included 18 patients with the peak stage 1 or 2 of the Bruce protocol, and weak stress intensity could cause a false negative for occurrence of PVCs during the recovery phase. The appropriate stress intensity for identifying risk of patients is unclear but the interpretation of results with low stress intensity should be careful.

## CONCLUSIONS

PVCs appeared as a bimodal increment during and after exercise in patients with Brugada syndrome. The occurrence of PVCs in the early recovery phase after the exercise was associated with VF events during follow-up, and it is a high-risk sign for VF. If these findings are confirmed in future studies, exercise testing should be a routine examination for risk stratification in Brugada syndrome, and patients with PVCs during the recovery phase should be referred to an electrophysiologist.

## ARTICLE INFORMATION

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### Disclosures

Drs Morita and Nishii are affiliated with the endowed department by Japan Medtronic Inc. The remaining authors have no disclosures to report.

### Supplementary Material

Tables S1–S2

Figures S1–S4

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Occurrence of PVCs associated with repeat exercise test.**

	Overall		VF+ (overall)		VF-		<i>p</i> value*
	307		33		274		
PVC (overall)	106	(34.5%)	15	(45.5%)	91	(33.2%)	0.1630
Rest	15	(4.9%)	1	(3.0%)	14	(5.1%)	0.6013
During exercise	19	(6.2%)	1	(3.0%)	18	(6.6%)	0.4261
Peak of exercise	64	(20.8%)	8	(24.2%)	56	(20.4%)	0.6118
Post 0 min	25	(8.1%)	4	(12.1%)	21	(7.7%)	0.3773
Post 1 min	19	(6.2%)	4	(12.1%)	15	(5.5%)	0.1350
Post 2 min	21	(6.8%)	6	(18.2%)	15	(5.5%)	0.0064
Post 3 min	13	(4.2%)	1	(3.0%)	12	(4.4%)	0.7166
Post 4 min	8	(2.6%)	0	(0%)	8	(2.9%)	0.3207
Post 5 min	4	(1.3%)	0	(0%)	4	(1.4%)	0.4855
Post (1.5–3.5 min)	26	(8.5%)	7	(21.2%)	19	(6.9%)	0.0055
Post (1.5–3.5) - (4–5)	20	(6.5%)	7	(21.2%)	13	(4.7%)	0.0003
PAC	70	(22.8%)	6	(20.0%)	64	(23.1%)	0.7007
PAT/PSVT	5	(1.6%)	0	(0%)	5	(1.8%)	0.4589
PAF	2	(0.7%)	0	(0%)	2	(0.7%)	0.6411

SSS	2	(0.7%)	0	(0%)	2	(0.7%)	0.6411
Paroxysmal AVB	1	(0.3%)	0	(0%)	1	(0.4%)	0.7421
CRBBB	2	(0.7%)	0	(0%)	2	(0.7%)	0.6411

\* Comparison patients with VF and without VF.

AVB: atrioventricular block, CRBBB: complete right bundle branch block, FH: family history, PAC: premature atrial complex, PAF:

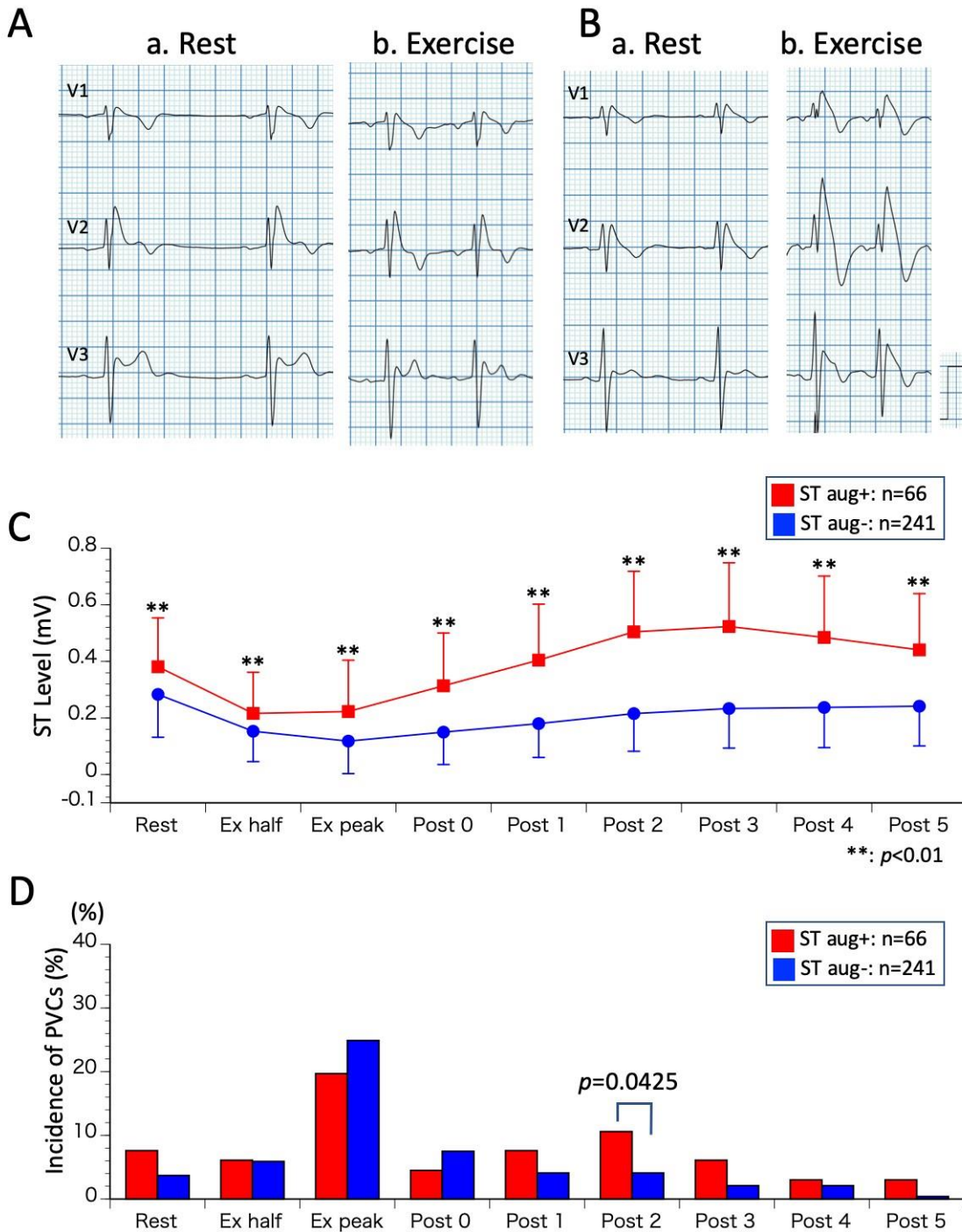
paroxysmal atrial fibrillation, PAT: paroxysmal atrial tachycardia, PSVT: paroxysmal supraventricular tachycardia, PVC: premature

ventricular complex, SD: sudden death, TMT: treadmill test, VF: ventricular fibrillation.

**Table S2. Univariable analysis of occurrence of PVCs associated with repeat exercise test for overall VF events.**

	Odds Ratio	CI	
PVC (overall)	1.68	0.81 - 3.48	0.1656
Rest	0.58	0.07 - 4.56	0.605
During exercise	0.44	0.06 - 3.44	0.4375
Peak of exercise	1.25	0.53 - 2.91	0.6118
Post 0 min	1.66	0.53 - 5.18	0.3810
Post 1 min	2.38	0.74 - 7.66	0.1453
Post 2 min	3.84	1.37 - 10.71	0.0102
Post 3 min	0.68	0.09 - 5.42	0.7177
Post 4 min	<0.01	-	0.9903
Post 5 min	<0.01	-	0.9896
Post (1.5–3.5min)	3.61	1.39 - 9.40	0.0084
Post (1.5–3.5) - (4–5)	5.41	1.98 - 14.74	0.0010

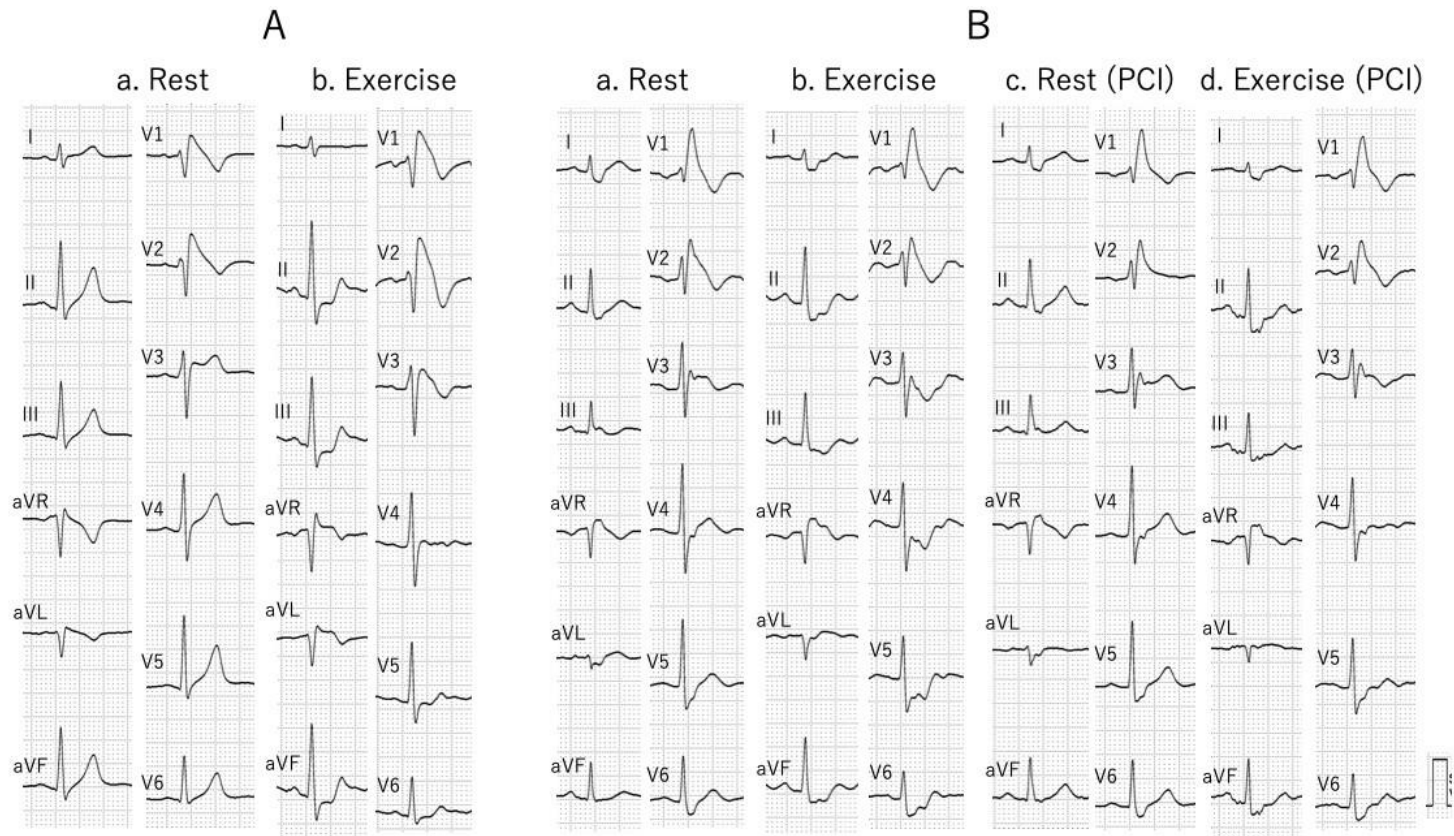
**Figure S1. ST augmentation after exercise.**



A. A patient without ST augmentation after exercise. B. A patient with ST augmentation after exercise. Leads V1–V3 showed significant ST augmentation after exercise. C. Changes of ST level during exercise (lead V2). ST level became minimum at the peak of exercise but increased during the recovery phase after exercise in 66 patients. About 80% of the patients did not have ST augmentation during the recovery phase. D. Occurrence of PVCs according to existence of ST augmentation after exercise. Patients with ST augmentation after exercise had more frequent PVCs at 2 min of the recovery phase than did patients without ST augmentation.

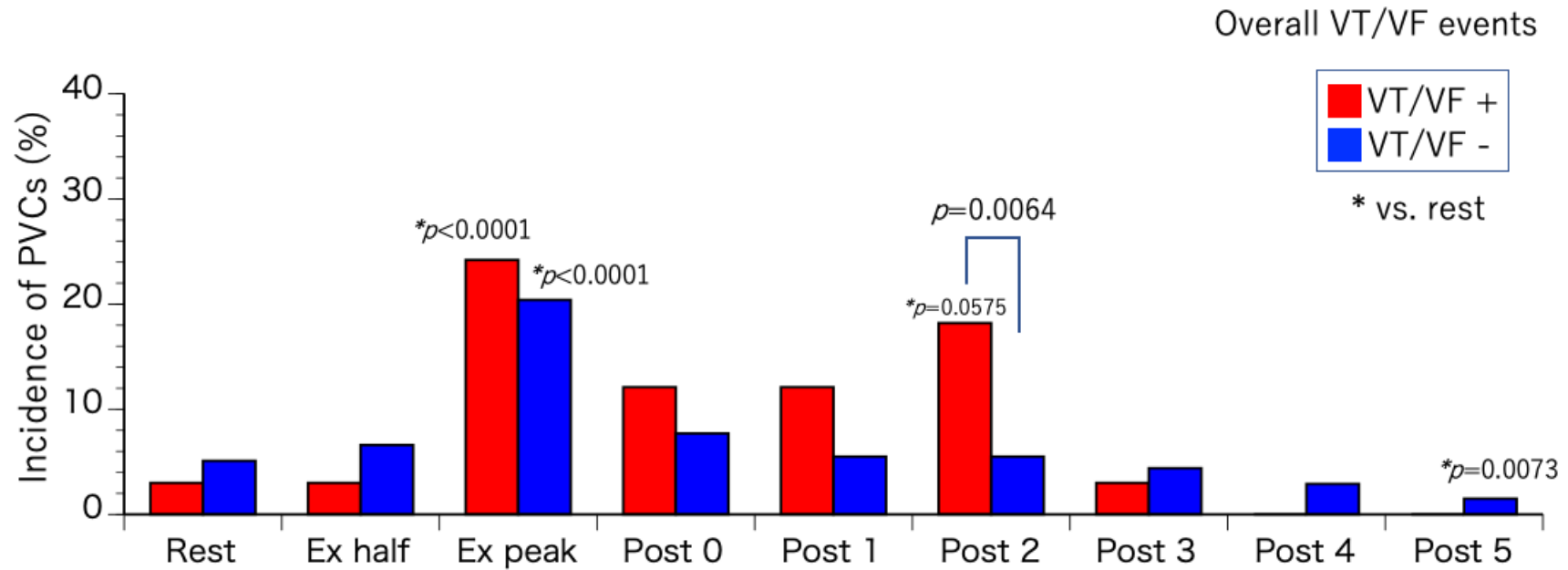


**Figure S2. ST depression after exercise.**



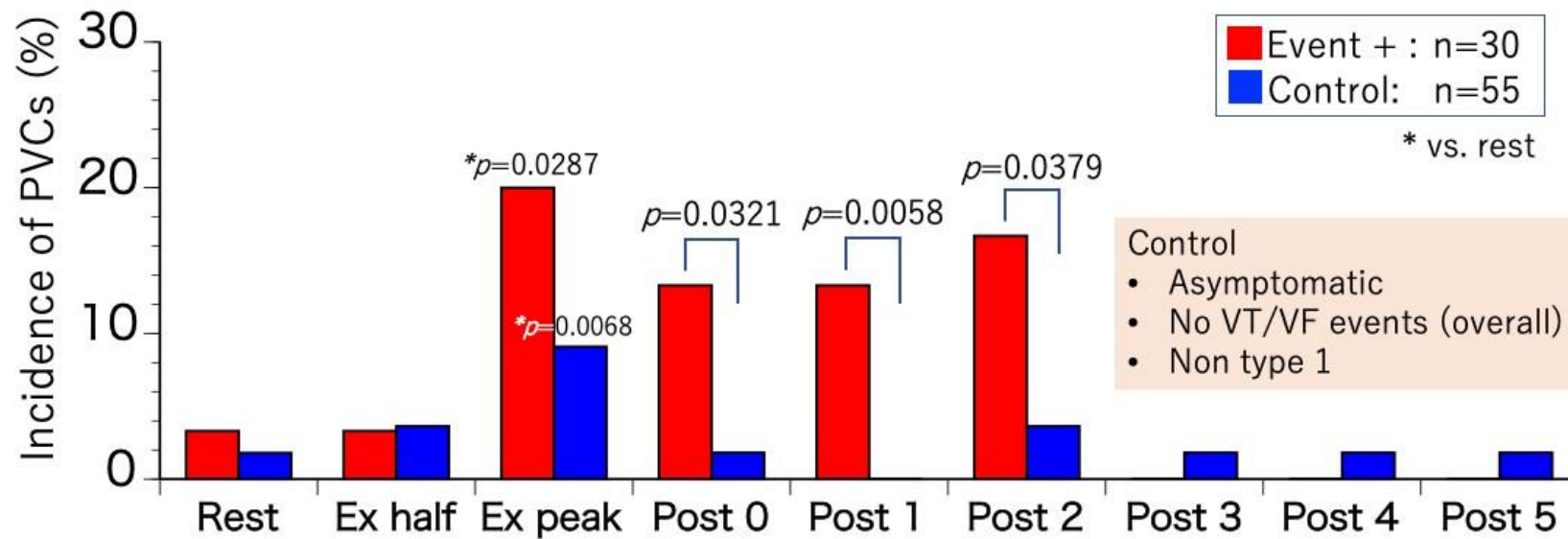
A. A patient who did not have coronary artery disease. Exercise induced ST depression in leads II, III, aVF, V5 and V6. B. A patient who had atherosclerotic stenosis in the right and left anterior descending coronary arteries. Exercise induced ST depression in leads II, III, aVF and V3–V6 (a and b). After percutaneous coronary intervention (PCI), exercise did not induce ST depression, but Brugada type ECG was persistent (c and d).

**Figure S3. Occurrence of PVCs during the exercise test including repeat treadmill tests.**



Patients who experienced VF previously or during follow-up frequently had PVCs at 2 min of the recovery phase compared to patients who never experienced VF.

Figure S4. Occurrence of PVCs in patients with VF events during follow-up and control patients.



Control patients were asymptomatic and did not experience VF during follow-up and did not have spontaneous type 1 ECG. Patients

with VF events more frequently had PVCs at 0–2 min of the recovery phase than did control patients.