

Prognostic Significance of the Sodium Channel Blocker Test in Patients With Brugada Syndrome

Akira Ueoka, MD; Hiroshi Morita, MD, PhD; Atsuyuki Watanabe, MD, PhD; Yoshimasa Morimoto, MD; Satoshi Kawada, MD; Motomi Tachibana, MD; Masakazu Miyamoto, MD; Koji Nakagawa, MD, PhD; Nobuhiro Nishii, MD, PhD; Hiroshi Ito, MD, PhD

Background—A drug provocation test using a sodium channel blocker (SCB) can unmask a type 1 ECG pattern in patients with Brugada syndrome. However, the prognostic value of the results of an SCB challenge is limited in patients with non-type 1 ECG. We investigated the associations of future risk for ventricular fibrillation with SCB-induced ECG changes and ventricular tachyarrhythmias (VTAs).

Methods and Results—We administered intravenous pilsicainide to 245 consecutive patients with Brugada syndrome (181 patients with spontaneous type 1 ECG, 64 patients with non-type 1 ECG). ECG parameters before and after the test and occurrence of drug-induced VTAs were evaluated. During a mean follow-up period of 113 ± 57 months, fatal VTA events occurred in 31 patients (sudden death: $n=3$, ventricular tachycardia/ventricular fibrillation: $n=28$). Symptomatic patients and spontaneous type 1 ECG were associated with future fatal arrhythmic events. Univariable analysis of ECG parameters after the test showed that long PQ and QRS intervals, high ST level, and SCB-induced VTAs were associated with later VTA events during follow-up. Multivariable analysis showed that symptomatic patients, high ST level ($V1 \geq 0.3$ mV after the test), and SCB-induced VTAs were independent predictors for future fatal arrhythmic events (hazard ratios: 3.28, 2.80, and 3.62, 95% confidence intervals: 1.54–7.47, 1.32–6.35, and 1.64–7.75, respectively; $P < 0.05$).

Conclusions—SCB-induced VTAs and ST-segment augmentation are associated with an increased risk of the development of ventricular tachycardia/ventricular fibrillation events during follow-up in patients with Brugada syndrome. (*J Am Heart Assoc.* 2018;7:e008617. DOI: 10.1161/JAHA.118.008617.)

Key Words: Brugada syndrome • risk stratification • sodium channel blocker • ventricular fibrillation

A sodium channel blocker (SCB) unmasks and augments type 1 ST elevation of Brugada syndrome (BrS). An SCB challenge is usually used to detect manifestation of type 1 ECG for diagnosis of BrS in patients with non-type 1 ECG.¹ The extents of PQ prolongation and QRS widening during the SCB test can be a clue for the existence of *SCN5A*

mutation.^{2–4} Although the SCB test is essential for diagnosis in non-type 1 patients, an unexpected response to administration of an SCB, such as atrioventricular block or ventricular tachyarrhythmias (VTAs), occasionally emerges in some patients.^{5,6}

The prognostic value of the results of an SCB challenge is limited in patients with BrS. Patients who have drug-induced type 1 ECG, with the exception of patients who have already experienced cardiac arrest, show a relatively benign clinical course compared with that for patients with spontaneous type 1 ECG.^{7–9} Patients in whom ECG was not converted to type 1 ECG by an SCB had a very good prognosis compared with that for patients with drug-induced type 1 ECG.¹⁰ SCB challenge only has diagnostic value in patients without spontaneous type 1 ECG. Moreover, the prognostic significance of an SCB challenge in patients with spontaneous type 1 ECG has not been evaluated. In fact, most investigators believe that an SCB test is contraindicated in patients with spontaneous type 1 ECG.

Recently, an SCB challenge has been used for detecting abnormal potentials on the epicardial surface of the right ventricle during epicardial catheter ablation. Symptomatic patients who have experienced arrhythmic syncope or

From the Departments of Cardiovascular Medicine (A.U., A.W., Y.M., S.K., M.T., M.M., K.N., H.I.), Cardiovascular Therapeutics (H.M., N.N.), Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Accompanying Table S1 and Figure S1 are available at <http://jaha.ahajournals.org/content/7/10/e008617/DC1/embed/inline-supplementary-material-1.pdf>

Correspondence to: Hiroshi Morita, MD, PhD, Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-Cho, Okayama 700-8558, Japan. E-mail: hmorita@cc.okayama-u.ac.jp

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Clinical Perspective

What Is New?

- Remarkable ST elevation and ventricular tachyarrhythmia induced by a challenge test with a sodium channel blocker were associated with arrhythmic events during follow-up in patients with Brugada syndrome.
- The prognostic value of a sodium channel blocker is applicable to patients with spontaneous type 1 ECG.
- The present study indicated the usefulness of a sodium channel blocker test in patients with spontaneous type 1 ECG for the first time.

What Are the Clinical Implications?

- A sodium channel blocker test can be used for (1) diagnosis of patients with non-type 1 ECG; (2) risk stratification in asymptomatic patients with spontaneous type 1 ECG; and (3) risk stratification in patients with spontaneous type 1 ECG and syncope of unknown cause.

documented VTA events have more advanced arrhythmogenic substrate on the epicardium.¹¹ If an SCB challenge can unmask concealed substrate in patients, ECG change and VTAs induced by the SCB will indicate progression of the substrate.

We hypothesized that remarkable ECG changes and VTAs provoked by an SCB challenge are associated with advanced arrhythmogenic substrate and that such changes are correlates of future VTA events in patients with BrS.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

The subjects of the present study were 245 consecutive patients with BrS who underwent a drug provocation test with pilsicainide in Okayama University Hospital (males: 240 patients, mean age: 46 ± 13 years). At the time of diagnosis, 154 patients were asymptomatic, 79 had syncope, and 12 had ventricular fibrillation (VF) (Table 1). We excluded obvious reflex syncope as a symptom and considered patients with reflex syncope as being asymptomatic. BrS was diagnosed when a type 1 ST-segment elevation appeared either spontaneously or after administration of an SCB. We defined spontaneous type 1 ECG as the appearance of type 1 ECG without any stress such as stress from fever or exercise. Type 1 ECG was defined as coved ST-segment elevation ≥ 2 mm in at least 1 right precordial lead in the second, third, or fourth intercostal space.¹² All 245 patients had spontaneous (n=181) or drug-induced type 1 ECG (n=64). To clarify the prognosis of patients with negative SCB and non-type 1, we also analyzed an additional 30 patients (29 males, age:

Table 1. Characteristics of Patients With Spontaneous and Drug-Induced Type 1 ECG

	Overall, n=245	P Value*
Clinical parameters		
Male	240 (98%)	...
Age, y	46.2±13.0	...
Symptomatic patients	91 (37%)	...
Syncope	79 (32%)	...
VT/VF	12 (5%)	...
Family history of SD	72 (29%)	...
SCN5A mutation	16/139 (12%)	...
VT/VF during follow-up	31 (13%)	...
ECG parameters		
Spontaneous type 1 ECG	181 (74%)	...
PQ interval lead II (ms)		
Pre SCB	180±27	<0.001
Post SCB	229±37	
QRS width (ms)		
V1		
Pre SCB	106±14	<0.001
Post SCB	133±23	
V2		
Pre SCB	107±14	<0.001
Post SCB	135±23	
ST level (mV)		
V1		
Pre SCB	0.158±0.106	<0.001
Post SCB	0.270±0.172	
V2		
Pre SCB	0.294±0.160	<0.001
Post SCB	0.591±0.277	
QTc interval (ms)		
V5		
Pre SCB	388±27	<0.001
Post SCB	427±35	
Drug-induced VTAs (n)		
Overall	24 (10%)	...
PVCs	13 (5%)	...
VTs	11 (4%)	...

PVCs indicates premature ventricular contractions; SCB, sodium channel blocker; SD, sudden death; VTA, ventricular tachyarrhythmia; VT/VF, ventricular tachycardia/ventricular fibrillation.

*P value: comparison of ECG parameters before and after the SCB test.

46±15 years) without positive SCB test who were suspected of having BrS (asymptomatic: 20 patients, syncope: 10 patients). There were no patients from the same family.

Echocardiography was performed in all patients, and no structural abnormalities were found.

All of the study protocols were approved by the Ethics Committee on Human Research and Epidemiology of Okayama University and Human Genome Studies of the Ethics Committee of Okayama University. Informed consent regarding data acquisition was obtained from all patients. Clinical data, including data on age, sex, family history of sudden cardiac death, history of syncope episodes, history of VF episodes, and the presence of *SCN5A* gene mutation were obtained from patient records. Analysis of *SCN5A* mutation was performed in 139 patients in compliance with the above guidelines.

The primary end point of this study was the occurrence of fatal VTA events defined as the occurrence of sudden cardiac death, VT or VF, and appropriate implantable cardioverter-defibrillator interventions during the follow-up period.

Pharmacologic Challenge Test

We performed an SCB test in an ECG laboratory or during electrophysiological study with a standby defibrillator and an emergency cart with medicines and intubation kit during hospitalization. Pilsicainide chloride was administered intravenously at a dose of 1 mg/kg over a period of 5 to 10 minutes in all patients. The difference between ECG parameters before and 15 minutes after administration of pilsicainide was calculated: PQ interval in lead II, QRS interval and ST level in leads V1 and V2, and QTc interval in lead V5. ST level was measured at the J points in leads V1, V2, and V5. Occurrence of severe VTAs after administration of pilsicainide was also evaluated. Severe VTAs during the test included frequent occurrence of premature ventricular contractions (PVCs) (>1 bpm) and polymorphic VT (at least 3 continuous beats). We stopped administration of pilsicainide if patients had significant QRS widening ($\geq 130\%$), second- or third-degree atrioventricular block, or occurrence of PVCs. If patients had severe ventricular arrhythmias, we observed the patients overnight in a cardiac care unit with or without isoproterenol infusion.

Statistical Analysis

Statistical analysis was performed using JMP 11.0 for MAC (SAS Institute Inc, Cary, NC). Data are expressed as means \pm SD or medians (interquartile range). Continuous variables in the different subgroups were analyzed by the Wilcoxon signed-rank test. We used the paired *t* test or the Wilcoxon signed-rank test to compare the values before and after the SCB test in the same patients. Categorical data and percentage frequencies were analyzed by the χ^2 test or Fisher test. Logistic regression analysis was conducted in order to identify predictive ECG parameters before and after the pilsicainide-challenge test. Receiver-operating characteristic

curves were constructed for ECG parameters to determine the optimal cutoff value for identifying patients with VF during follow-up. Event rate curves were plotted according to the Kaplan–Meier method and were analyzed by the log-rank test. Univariate and multivariate Cox regression analyses were performed to assess whether each index can be a significant and independent predictor of fatal arrhythmic events. We used the following covariates for multivariable analysis: important baseline characteristics (symptoms and spontaneous type 1 ECG) and ECG parameters after the pilsicainide test (PQ and QRS intervals, ST level, and pilsicainide-induced VTAs). A value of $P < 0.05$ was considered statistically significant.

Results

Characteristics of Patients and Results of the Pilsicainide Test

Baseline characteristics of the patients according to clinical presentation are summarized in Table 1. Spontaneous type 1 ECG was observed in 74% of the patients. Thirty-two percent of the patients had a history of syncope episodes and 5% of the patients had previous VF episodes. Gene analysis was performed in 139 patients, and *SCN5A* gene mutation was found in 12% of the patients.

The reasons for performing the pilsicainide test were diagnosis of BrS in patients without spontaneous type 1 ECG ($n=62$), confirmation of type 1 ECG in patients who transiently had type 1 ECG with or without specific conditions (such as fever, after exercise, or after taking medicine, $n=2$), detection of an abnormal endocardial or epicardial electrogram or induction of PVCs during electrophysiological study and/or catheter ablation ($n=131$), and possibility of risk stratification for detecting abnormal ECGs such as T-wave alternans ($n=50$).^{13,14} The reasons for performing the SCB test in patients with nonspontaneous type 1 ECG were existence of ECG abnormality (35 asymptomatic patients) and existence of syncope (26 patients) or VF (3 patients).

Administration of pilsicainide unmasked type 1 ECG in all of the 64 patients who did not have spontaneous type 1 ECG. ST level was significantly augmented after the pilsicainide test (Table 1). Pilsicainide prolonged PQ, QRS, and QTc intervals. Pilsicainide induced VTAs in 24 patients (Figure 1), including frequent PVCs in 13 patients (Figure 2A) and VT/VF in 11 patients (Figures 2B and 3, Tables 1 and 2). Cardioversion was required to terminate VT/VF in 4 patients (external defibrillator: $n=3$, implantable cardioverter-defibrillator: $n=1$). None of the patients had prolonged VT/VF episodes. One patient developed transient complete atrioventricular block. Patients with pilsicainide-induced VTA more frequently had spontaneous type 1 ECG, higher ST level after the test (V1), and longer QT interval than did patients without pilsicainide-induced VTA (Table 3).

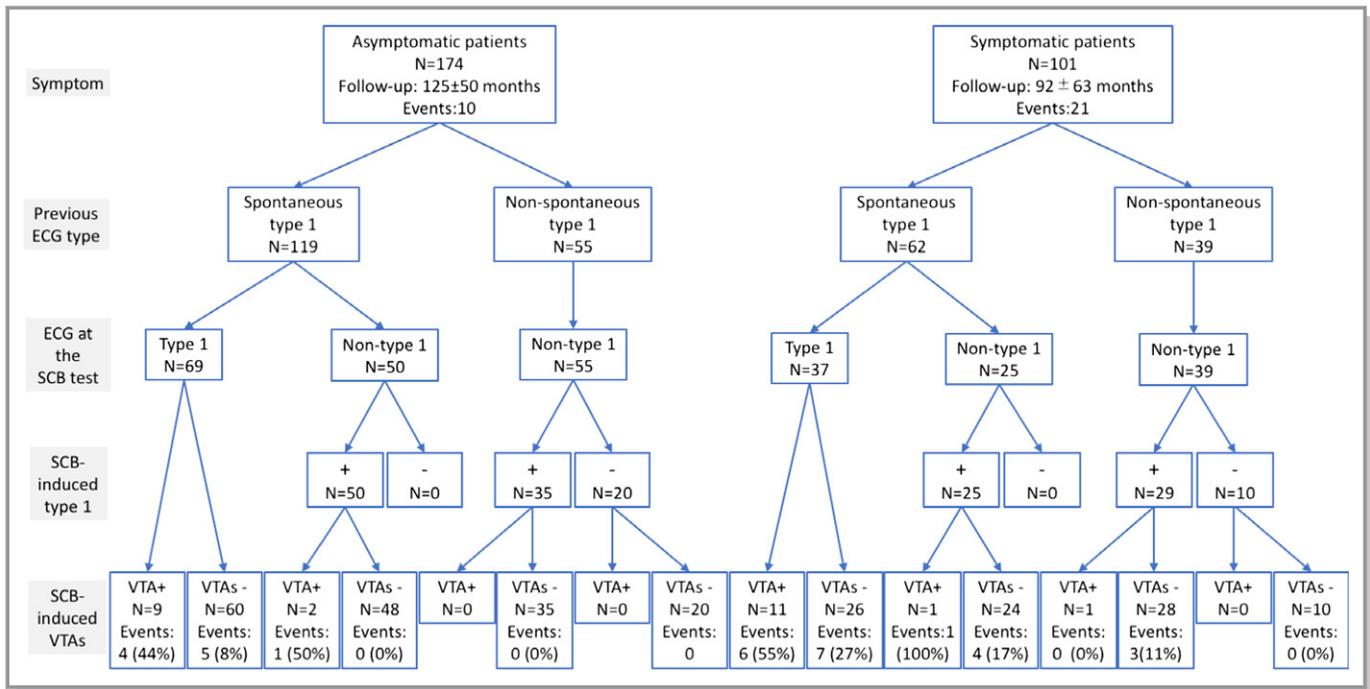


Figure 1. Results of pilsicainide tests and occurrence of cardiac events. The groups of patients consisted of 245 patients with spontaneous or drug-induced type 1 ECG and 30 patients with non-type 1 ECG that was not converted to type 1 ECG by a sodium channel blocker (SCB). The results were divided according to the symptom, ECG type, ECG type at the pilsicainide test, result of the pilsicainide test, and occurrence of pilsicainide-induced ventricular arrhythmias (VTAs).

During a mean follow-up period of 113 ± 57 months, fatal VTA events occurred in 31 patients. Three patients died suddenly, 26 experienced VF (implantable cardioverter-defibrillator shock in 24 patients, aborted cardiac arrest in 2 patients), and 2 developed monomorphic VTs. The time to a fatal VTA event was shorter in patients with spontaneous type 1 ECG than in patients without spontaneous type 1 ECG (Figure 4A), and the same result was observed in patients' subgroups according to symptoms (Figure 4B). There was no VTA event in patients without a positive SCB test. Patients with pilsicainide-induced VTA had more frequent fatal VTA events during follow-up (12/24, event ratio: 7.1%/y) than did patients without pilsicainide-induced VTA (19/221, event ratio: 0.89%, $P < 0.0001$) (Figure 4C). There was no difference in fatal VTA events during follow-up between patients with pilsicainide-induced VT/VF (5/11, event ratio: 6.3%) and patients with pilsicainide-induced PVCs only (7/13, event ratio: 7.9%, $P = 0.6820$).

Changes in ECG Parameters and Occurrence of Ventricular Arrhythmias Induced by Pilsicainide in Different Subgroups of Patients

Pilsicainide significantly prolonged QRS interval and significantly augmented ST elevation in patients with spontaneous type 1 ECG compared with those in patients without

spontaneous type 1 ECG (Table 4). At the time of the SCB test, 75 patients (41%) in whom spontaneous type 1 ECG was recorded previously did not show spontaneous type 1 ECG at the beginning of the test. Pilsicainide provoked type 1 ECG in those patients (Figure 1). PQ and QTc intervals before and after the pilsicainide test were not different between patients with and without spontaneous type 1 ECG. Pilsicainide more frequently induced VTAs in patients with spontaneous type 1 ECG than in patients without spontaneous type 1 ECG (Table 4).

Symptomatic patients had a longer PQ interval but had a lower ST level in V2 than did asymptomatic patients at baseline (Table 5). There were no differences in other ECG parameters between asymptomatic and symptomatic patients at baseline. Pilsicainide significantly prolonged PQ and QRS intervals in leads V1 and V2 in symptomatic patients compared with those in asymptomatic patients. ST level in lead V2 in asymptomatic patients was higher than that in symptomatic patients after pilsicainide administration. Pilsicainide-induced VT/VF was more frequent in symptomatic patients than in asymptomatic patients (Table 5).

Patients with *SCN5A* mutation ($n = 16$) had longer PQ interval before the pilsicainide test than did patients without *SCN5A* mutation ($n = 123$) (Table S1). After administration of pilsicainide, patients with *SCN5A* mutation had significantly longer PQ and QRS intervals than did patients without *SCN5A*

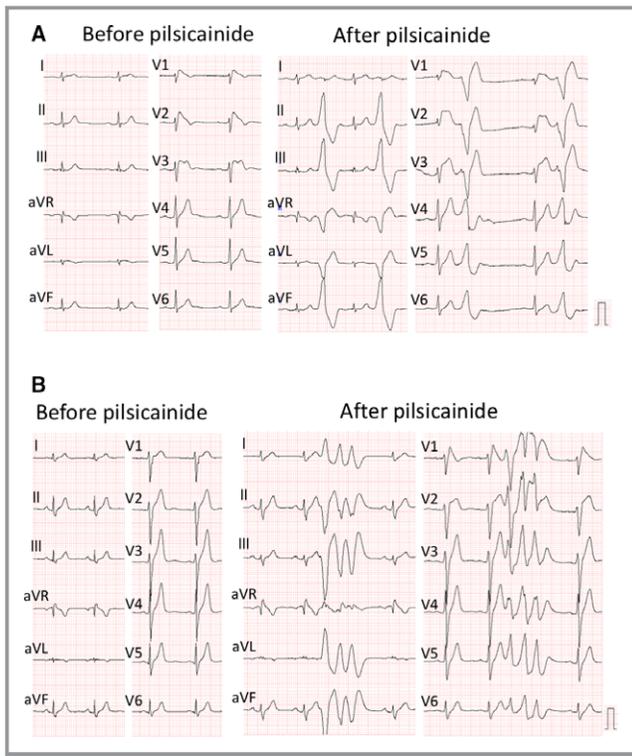


Figure 2. Pilsicainide-induced ventricular arrhythmia. A, These ECGs were recorded in a patient with syncope (50 years old). The left panel shows ECG at baseline. Leads V1-2 were located at the third intercostal space. The patient had spontaneous type 1 ECG only in the leads at high intercostal spaces. The right panel shows that pilsicainide provoked frequent occurrence of premature ventricular contractions and significant ST elevation. B, These ECGs were recorded in an asymptomatic patient (27 years old). The patient had fever-induced type 1 ECG but did not have spontaneous type 1 ECG. The left panel shows non-type 1 ECG before the pilsicainide test. Leads V1-2 were recorded at regular lead positions. The right panel shows that pilsicainide induced nonsustained polymorphic ventricular tachycardia. The patient died suddenly at night 6 years after the test.

mutation. There were no differences in prevalence of drug-induced VTAs and other ECG parameters before and after the pilsicainide test between patients with and without *SCN5A* mutation.

Risk Factors for VT/VF Events During Follow-Up

Table 6 shows results of univariable analysis of clinical and ECG parameters before and after the pilsicainide test to detect VTA events during follow-up. Univariable analysis of clinical parameters showed that symptomatic patients, especially those with previous episodes of VT/VF, were associated with fatal arrhythmic events during follow-up. In ECG parameters before the pilsicainide test, QRS intervals in leads V1 and V2 were associated with cardiac events. Univariable analysis of ECG parameters after the pilsicainide test to

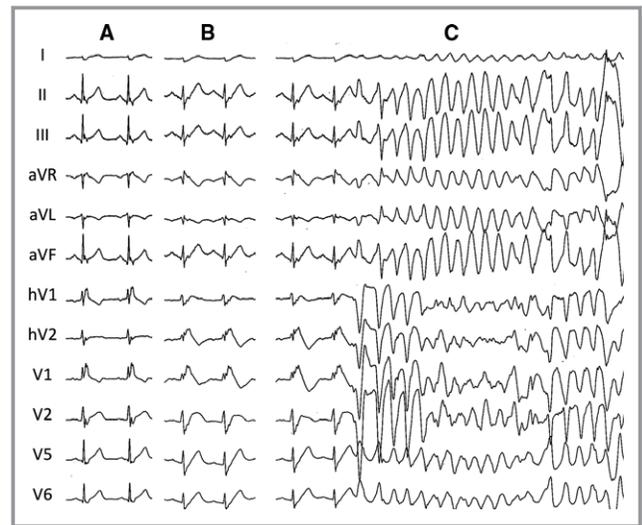


Figure 3. Pilsicainide-induced polymorphic ventricular tachycardia and ventricular fibrillation. These ECGs were recorded in a 50-year-old patient with ventricular fibrillation (VF). A, ECG at baseline. The patient had spontaneous type 1 ECG, but ST elevation was diminished before the test. We performed a pilsicainide test to unmask the abnormal electrical substrate during electrophysiological study. Pilsicainide provoked type 1 ECG (B) and VF (C). A direct current shock was required to terminate VF.

detect VTA events showed that PQ interval, QRS intervals (V1 and V2), and ST level (V1) were associated with fatal arrhythmic events during follow-up. Among the differences between ECG parameters before and after the pilsicainide test, differences in PQ interval (Δ PQ) and ST level (Δ ST) in V1 were predictors of VT/VF events. Drug-induced VTAs were also associated with fatal arrhythmic events during follow-up, but there was no difference in prediction of fatal events between drug-induced PVCs and drug-induced VT/VF.

Cutoff points of ECG parameters after the pilsicainide test to detect fatal arrhythmic events during follow-up were determined by receiver-operating characteristic analysis: PQ interval ≥ 235 ms (area under the curve: 0.663), QRS interval in lead V1 ≥ 132 ms (area under the curve: 0.693), and ST level in lead V1 ≥ 0.3 mV (area under the curve 0.671) were optimal cutoff points (Figure S1). Univariable analysis of these parameters showed that they were associated with fatal VTA events: the hazard ratio (HR) of PQ interval ≥ 235 ms was 3.16 (95% confidence interval [CI], 1.54–6.85, $P=0.0021$), HR of QRS interval ≥ 132 ms was 4.22 (95% CI, 1.97–10.06, $P=0.0005$), and HR of ST level ≥ 0.3 mV was 4.03 (95% CI, 1.95–8.94, $P=0.0003$). When we focused on the asymptomatic patients, ST level after pilsicainide ≥ 0.3 mV (HR: 1.7, CI, 3.1–325.5, $P=0.0002$) and drug-induced VTAs (HR: 15.6, CI, 4.3–56.1, $P=0.0001$) were also predictors of VT/VF events during follow-up.

Table 2. Patients With Pilsicainide-Induced Ventricular Arrhythmia

Patients	Age (y)	Sex	Spontaneous Type 1	Clinical Presentation	FH of SD	VF Induction by PES	SCN5A Mutation	Type of SCB-VTA	ICD Implantation During Follow-Up	VTA During Follow-Up
1	50	Male	Yes	Asymptomatic	Yes	Yes	No	Frequent PVC	No	Sustained VT
2	27	Male	Yes	Asymptomatic	No	Yes	No	Frequent PVC	No	None
3	55	Male	Yes	Syncope	No	Yes	No	VF	Yes	Appropriate ICD shock
4	41	Male	Yes	VF	No	Yes	No	NSVT	Yes	Appropriate ICD shock
5	55	Male	Yes	VF	Yes	Yes	No	Frequent PVC	Yes	Appropriate ICD shock
6	42	Male	No	VF	No	Yes	No	Frequent PVC	Yes	None
7	41	Male	Yes	Syncope	No	No	No	NSVT*	Yes	None
8	57	Male	Yes	Asymptomatic	No	No	No	Frequent PVC	No	None
9	47	Male	Yes	Syncope	Yes	No	Yes	Frequent PVC	Yes	Appropriate ICD shock
10	29	Male	Yes	Syncope	Yes	No	Yes	Sustained VT*	No	None
11	40	Male	Yes	Asymptomatic	Yes	Yes	No	NSVT	Yes	None
12	50	Male	Yes	Syncope	No	Yes	No	VF	Yes	Appropriate ICD shock
13	42	Male	Yes	Asymptomatic	No	Yes	No	Frequent PVC	Yes	Appropriate ICD shock
14	38	Male	Yes	Asymptomatic	Yes	Yes	No	Frequent PVC	No	None
15	34	Male	Yes	Syncope	Yes	Yes	No	Frequent PVC	Yes	Appropriate ICD shock
16	38	Male	Yes	Syncope	No	No	Yes	NSVT	No	None
17	50	Male	Yes	Asymptomatic	No	Yes	NA	NSVT*	Yes	None
18	27	Male	Yes	Asymptomatic	Yes	Yes	No	NSVT	No	SD
19	50	Male	Yes	Syncope	No	Yes	NA	Sustained VT	No	VF
20	36	Male	Yes	Syncope	Yes	Yes	No	NSVT	Yes	None
21	74	Male	Yes	Asymptomatic	Yes	Yes	NA	Frequent PVC	Yes	Sustained VT
22	36	Male	Yes	Asymptomatic	No	Yes	NA	Frequent PVC	Yes	Appropriate ICD shock
23	25	Male	Yes	Syncope	No	No	Yes	VT*/VF	Yes	Appropriate ICD shock
24	41	Male	Yes	Asymptomatic	No	Yes	NA	Frequent PVC	No	None

FH indicates family history; ICD, implantable cardioverter defibrillator; NA, not assessed; NSVT, nonsustained ventricular tachycardia; PES, programmed electrical stimulation; PVC, premature ventricular contraction; SCB, sodium channel blocker; SD, sudden death; VF, ventricular fibrillation; VT, ventricular tachycardia; VTA, ventricular tachyarrhythmia.

*VT with wide QRS complex and not significant polymorphic change.

Multivariable analysis of baseline characteristics (symptoms and spontaneous type 1 ECG) and ECG parameters after the pilsicainide test (PQ and QRS intervals, ST level, and pilsicainide-induced VTAs) showed that symptoms, ST level after the pilsicainide test, and drug-induced VTAs were independent risk factors for fatal arrhythmic events during follow-up (Table 7). Patients with high ST level in lead V1 after the pilsicainide test or drug-induced VTAs had a shorter time to fatal events than did patients without these parameters (Figure 4C and 4D).

Discussion

New Findings

The present study showed that high ST level in lead V1 after the pilsicainide test and drug-induced VTAs were associated

with VT/VF events. These risk factors detected by the SCB test were independent predictors of cardiac events even after adjustment by the presence of symptoms and spontaneous type 1 ECG. There has been no report of ECG changes after an SCB test other than the appearance of drug-induced type 1 ECG having prognostic value. The results of the present study showed that an SCB test is useful as a risk stratification tool in patients with spontaneous type 1 ECG in addition to being a diagnostic tool in patients without spontaneous type 1 ECG.

Occurrence and Prognostic Value of SCB-Induced Ventricular Arrhythmias

Previous studies showed that an SCB test induced VTAs in 0% to 25% of patients and VF in up to 4% of patients with BrS.^{13,15–34} The incidence of SCB-induced VTAs increased if the subjects of the study included subjects with spontaneous

Table 3. Different Characteristics of Patients With and Those Without SCB-Induced VTAs

	Pilsicainide-Induced VTA+ (n=24)	Pilsicainide-Induced VTA- (n=221)	P Value*
Clinical parameters			
Male	24 (100%)	216 (98%)	1.0000
Age, y	42.7±11.3	46.6±13.2	0.1478
Symptomatic patients	13 (54%)	78 (35%)	0.0782
Syncope	9 (38%)	70 (32%)	0.6464
VT/VF	4 (17%)	8 (4%)	0.0207
Family history of SD	10 (42%)	62 (28%)	0.1659
SCN5A mutation	4/20 (20%)	12/119 (10%)	0.2386
VT/VF during follow-up	12 (50%)	19 (9%)	<0.0001
ECG parameters			
Spontaneous type 1 ECG	23 (96%)	158 (71%)	0.0068
PQ interval in lead II (ms)			
Pre SCB	185±26	180±27	0.3227
Post SCB	242±43	227±36	0.0578
QRS width (ms)			
V1			
Pre SCB	113±22	105±13	0.0969
Post SCB	145±36	131±21	0.0576
V2			
Pre SCB	114±21	106±13	0.0429
Post SCB	146±33	134±22	0.0748
ST level (mV)			
V1			
Pre SCB	0.200±0.132	0.153±0.102	0.0307
Post SCB	0.385±0.219	0.257±0.162	0.0037
V2			
Pre SCB	0.307±0.194	0.293±0.157	0.9613
Post SCB	0.599±0.295	0.91±0.276	0.8236
QTc interval (ms)			
V5			
Pre SCB	387±29	388±27	0.8371
Post SCB	450±43	424±33	0.0046

All patients had type 1 ECG spontaneously or by SCB. SCB indicates sodium channel blocker; SD, sudden death; VTA, ventricular tachyarrhythmia; VT/VF, ventricular tachycardia/ventricular fibrillation.

*P value: comparison of ECG parameters in patients with and without pilsicainide-induced VTAs.

type 1 ECG. In the present study, 10% of the patients developed VT/VF or frequent PVCs after administration of pilsicainide, and the incidence of SCB-induced VTAs coincided with that in previous studies that included subjects with spontaneous type 1 ECG.

We showed that pilsicainide-induced VTA was a powerful predictor of VT/VF after adjustment of symptoms and ECG type. Some studies have shown that SCB-induced VTAs failed to predict VT/VF events during follow-up.^{19,27,34} However, those studies included a small number of patients or only patients without spontaneous type 1 ECG. The present study included patients with spontaneous type 1 ECG (74%), and the occurrence of SCB-induced VTAs in patients without spontaneous type 1 ECG was less frequent than that in patients with spontaneous type 1 ECG. Then the prognostic value of SCB-induced VTAs should be significant in patients with spontaneous type 1 ECG. Recently, an SCB test has been used to unmask concealed substrate at the time of epicardial ablation.¹¹ Application of radiofrequency energy to all abnormal substrate is necessary to eliminate the arrhythmogenic area. ECG changes similar to those induced by an SCB test can appear during febrile illness,³⁵ and VTA events also occur at that time. Thus, VTAs induced by an SCB test are not proarrhythmic effects but represent concealed arrhythmogenic substrate that can appear in daily life.

Some asymptomatic patients without spontaneous type 1 ECG might have false-positive results of the SCB test.^{36,37} This study included 35 asymptomatic patients with nonspontaneous type 1 ECG that was converted to type 1 ECG by the pilsicainide test (Figure 1). This group of patients was diagnosed as “possible” BrS by a new scoring system,³⁸ and some of those patients might be false positive. However, those patients did not have pilsicainide-induced VTAs and did not have cardiac events during follow-up. Thus, SCB-induced VTAs would indicate that the patients have “definite” BrS³⁸ with a more progressive arrhythmogenic substrate.

Risk and Safety of an SCB Test in Patients With Type 1 ECG

An SCB test is useful and safe for most patients, but some studies have shown that some patients develop severe VTAs requiring external defibrillation, implantable cardioverter-defibrillator therapy, or an extracorporeal membrane oxygenator.^{6,13,15,19,23,28,31,34} An SCB test should be performed during hospitalization, and continuous infusion of low-dose isoproterenol after the test should be performed overnight for high-risk patients. To avoid catastrophic events, it was stated in the Consensus report that an SCB test should be discontinued in cases of frequent PVCs and QRS

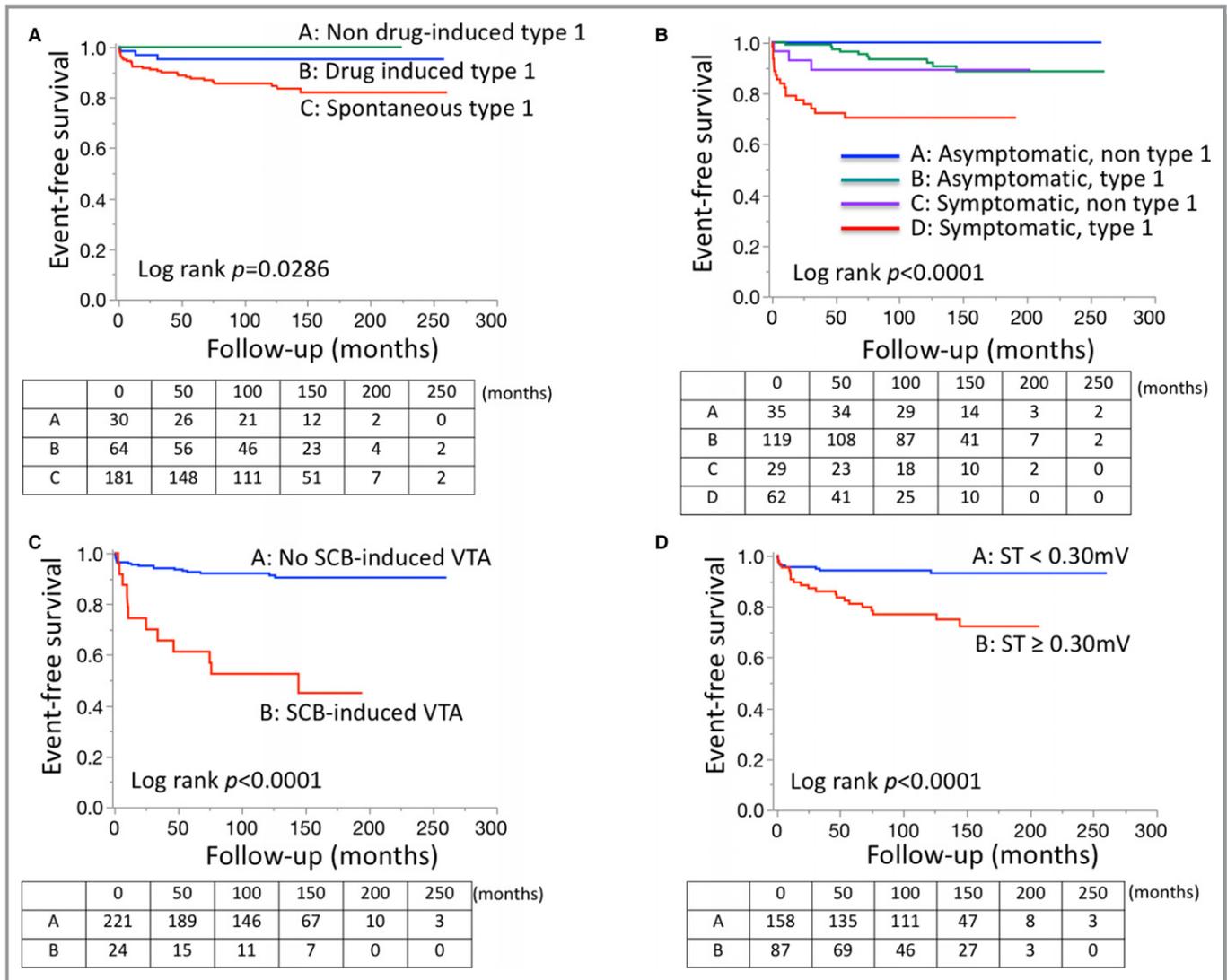


Figure 4. Kaplan–Meier analysis of fatal arrhythmic events. A, Event-free survival by ECG types including non–type 1, drug-induced type 1, and spontaneous type 1. Patients with spontaneous type 1 ECG had a worse prognosis than did patients without spontaneous type 1 ECG. No arrhythmic event occurred in patients without type 1 ECG. B, Event-free survival by symptoms and ECG types in patients with spontaneous or drug-induced type 1 ECG. Symptomatic patients more frequently experienced arrhythmic events than did asymptomatic patients. C, Event-free survival by pilsicainide-induced ventricular tachyarrhythmias (VTAs) in patients with spontaneous or drug-induced type 1 ECG. Pilsicainide-induced VTAs were associated with increased risk of fatal arrhythmic events. D, Event-free survival by degree of ST elevation in patients with spontaneous or drug-induced type 1 ECG. Patients with marked ST elevation (≥ 0.3 mV) in lead V1 after administration of pilsicainide had a significantly higher risk of fatal arrhythmic events than did patients with less ST elevation. Tables under the survival curve show the number of patients at risk. SCB indicates sodium channel blocker.

widening.³⁸ The present study showed that high ST level and prolonged QT interval after the test occurred in patients with pilsicainide-induced VTAs (Table 3), and these ECG changes can be warning signs of drug-induced VTAs. Since most of the pilsicainide-induced VTAs occurred in patients with spontaneous type 1 ECG, an SCB test should be performed in such patients with meticulous caution regarding ECG changes during the test.

Based on the results of this study, we consider that the criteria for performing an SCB test are (1) diagnosis of

patients with non–type 1 ECG; (2) risk stratification in asymptomatic patients with spontaneous type 1 ECG; and (3) risk stratification in patients with spontaneous type 1 ECG and syncope of unknown cause.

Limitations

Female sex is a possible risk for arrhythmic events during an SCB test.⁶ We could not determine sex risk of the SCB test in this study because we performed the test in only 5 female

Table 4. Differences Between Patients With Spontaneous and Drug-Induced Type 1 ECG

	Spontaneous Type 1 (n=181)	Drug-Induced type1 (n=64)	P Value*
Clinical parameters			
Male	179 (99%)	61 (95%)	0.1135
Age, y	46.0±12.9	46.8±13.5	0.5918
Symptomatic patients	62 (34%)	29 (45%)	0.133
Syncope	53 (29%)	26 (41%)	0.1194
VT/VF	9 (5%)	3 (5%)	1.0000
Family history of SD	56 (31%)	16 (25%)	0.4265
SCN5A mutation	13/109 (12%)	3/30 (10%)	1.0000
VT/VF during follow-up	28 (15%)	3 (5%)	0.0257
ECG parameters			
Spontaneous type 1 ECG	181 (100%)	0	...
PQ interval in lead II (ms)			
Pre SCB	181±27	180±25	0.9877
Post SCB	230±38	226±35	0.4217
QRS width (ms)			
V1			
Pre SCB	108±14	101±14	0.0004
Post SCB	134±23	128±22	0.0085
V2			
Pre SCB	108±14	102±14	0.0011
Post SCB	136±23	130±25	0.0041
ST level (mV)			
V1			
Pre SCB	0.180±0.111	0.096±0.059	<0.0001
Post SCB	0.303±0.182	0.177±0.094	<0.0001
V2			
Pre SCB	0.331±0.163	0.190±0.094	<0.0001
Post SCB	0.644±0.276	0.444±0.226	<0.0001
QTc interval (ms)			
V5			
Pre SCB	387±27	392±27	0.2183
Post SCB	427±36	425±31	0.7757
Drug-induced VTA (n)			
Overall	23 (13%)	1 (2%)	0.0068
PVCs	12 (7%)	1 (2%)	0.193
VTs	11 (6%)	0 (0%)	0.071

PVCs indicates premature ventricular contractions; SCB, sodium channel blocker; SD, sudden death; VTA, ventricular tachyarrhythmia; VT/VF, ventricular tachycardia/ventricular fibrillation.

*P value: comparison of ECG parameters in patients with and those without spontaneous type 1 ECG.

Table 5. Characteristics of Patients With Symptoms at Initial Visit to the Hospital

Symptoms	Asymptomatic (n=154)	Symptomatic (n=91)	P Value*
Clinical parameters			
Male	151 (98%)	89 (98%)	1
Age, y	46.3±13.4	46.0±12.4	0.9576
Symptomatic patients	0	91	...
Syncope	0	79	...
VT/VF	0	12	...
Family history of SD	51 (33%)	21 (23%)	0.1110
SCN5A mutation	6/80 (8%)	10/59 (17%)	0.1121
VT/VF during follow-up	10 (6%)	21 (23%)	0.0003
ECG parameters			
Spontaneous type 1 ECG	119 (77%)	62 (68%)	0.133
PQ interval in lead II (ms)			
Pre SCB	177±24	187±29	0.0084
Post SCB	223±34	238±40	0.0027
QRS width (ms)			
V1			
Pre SCB	105±12	107±18	0.8629
Post SCB	130±20	137±27	0.02
V2			
Pre SCB	106±11	108±18	0.7396
Post SCB	131±21	140±26	0.0026
ST level (mV)			
V1			
Pre SCB	0.162±0.109	0.151±0.102	0.4899
Post SCB	0.273±0.174	0.264±0.171	0.8308
V2			
Pre SCB	0.319±0.164	0.251±0.145	0.0012
Post SCB	0.634±0.282	0.520±0.256	0.0025
QTc interval (ms)			
V5			
Pre SCB	386±28	392±26	0.1491
Post SCB	424±35	432±35	0.0837
Drug-induced VTA (n)			
Overall	11 (7%)	13 (14%)	0.0782
PVCs	8 (5%)	5 (5%)	1
VTs	3 (2%)	8 (9%)	0.0213

All patients had type 1 ECG spontaneously or by SCB. PVCs indicates premature ventricular contractions; SCB, sodium channel blocker; SD, sudden death; VTA, ventricular tachyarrhythmia; VT/VF, ventricular tachycardia/ventricular fibrillation.

*P value: comparison of ECG parameters in asymptomatic patients and symptomatic patients.

Table 6. HR for Predicting VTA Events

	HR	95% CI	P Value
Clinical parameters			
Male	0.62	0.13 to 10.98	0.6588
Age, y	0.99	0.96 to 1.02	0.5741
Symptomatic patients	4.35	2.10 to 9.67	<0.0001
Syncope	1.49	0.70 to 3.05	0.2851
VT/VF	13.81	5.97 to 29.39	<0.0001
Family history of SD	1.12	0.51 to 2.32	0.7657
SCN5A mutation	1.90	0.64 to 4.62	0.2253
ECG parameters			
Spontaneous type 1 ECG	3.72	1.09 to 12.69	0.0279
PQ interval in lead II			
Pre SCB	1.01	0.99 to 1.02	0.3054
Post SCB	1.01	1.00 to 1.02	0.0006
Δ PQ	1.02	1.01 to 1.03	0.0066
QRS width			
V1			
Pre SCB	1.03	1.01 to 1.04	0.0109
Post SCB	1.01	1.00 to 1.02	0.0155
Δ QRS	1.01	0.99 to 1.02	0.2221
V2			
Pre SCB	1.03	1.01 to 1.04	0.0059
Post SCB	1.01	1.00 to 1.02	0.0157
Δ QRS	1.01	0.99 to 1.02	0.2798
ST level			
V1			
Pre SCB	7.69	0.33 to 118.40	0.1914
Post SCB	11.43	2.03 to 54.72	0.0069
Δ ST	12.14	1.55 to 66.11	0.0087
V2			
Pre SCB	0.78	0.07 to 6.84	0.8348
Post SCB	0.64	0.16 to 2.34	0.512
Δ ST	0.56	0.10 to 2.85	0.499
QTc interval			
V5			
Pre SCB	1	0.99 to 1.01	0.8812
Post SCB	1.01	1.00 to 1.01	0.3075
Δ QT	1.01	0.99 to 1.02	0.1736

Continued

patients (2%). PVC/VT did not occur in all of the female patients. We did not avoid performing an SCB test for female patients. A high prevalence of males (>90% of the patients) with BrS was frequently observed in previous

Table 6. Continued

	HR	95% CI	P Value
Drug-induced VTA			
Overall	6.95	3.28 to 14.19	<0.0001
PVCs	6.36	2.53 to 14.05	0.0003
VTs	4.66	1.57 to 11.17	0.0082

HR of the ECG parameters represents risk increase/1 unit. CI indicates confidence interval; HR, hazard ratio for predicting VT/VF; PVCs, premature ventricular contractions; SCB, sodium channel blocker; SD, sudden death; VTA, ventricular tachyarrhythmia; VT/VF, ventricular tachycardia/ventricular fibrillation.

Japanese studies,^{27,39} and it might be a racial characteristic of BrS.

Conclusion

VTAs and augmentation of ST-segment elevation after an SCB challenge test were associated with an increased risk of the development of VT/VF events in patients with BrS, especially in patients with spontaneous type 1 ECG. An SCB challenge test can serve as not only a diagnostic tool in patients without spontaneous type 1 ECG but also a risk stratification tool for patients with spontaneous type 1 ECG.

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Table 7. Multivariable Analysis of Clinical and ECG Parameters for Predicting VTA Events

	HR	95% CI	P Value
Baseline clinical parameters			
Symptomatic patients	3.28	1.54 to 7.47	0.0019
Spontaneous type 1 ECG	1.76	0.57 to 7.78	0.3496
ECG parameters after SCB test			
PQ interval \geq 235 ms	1.60	0.73 to 3.65	0.2399
QRS interval \geq 132 ms	2.22	0.98 to 5.53	0.0559
ST level \geq 0.3 mV	2.80	1.32 to 6.35	0.0067
SCB-induced VTAs	3.62	1.64 to 7.75	0.0019

CI indicates confidence interval; HR, hazard ratio; SCB, sodium channel blocker; VTA, ventricular tachyarrhythmia.

Disclosures

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

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SUPPLEMENTAL MATERIAL

Table S1. Different characteristics of patients with and those without SCN5A mutations.

			SCN5A (+)	SCN5A (-)		
			n = 16	n = 123	<i>p</i> value	
Clinical parameters	Male	(patients)	16 (100%)	120 (98%)	1.0000	
	Age	(years)	40.9 ± 17.4	45.7 ± 11.6	0.3032	
	Symptomatic patients	(patients)	10 (63%)	49 (40%)	0.0948	
	Syncope	(patients)	8 (50%)	41 (33%)		
	VT/VF	(patients)	2 (13%)	8 (7%)	0.2973	
	Family history of SD	(patients)	7 (44%)	44 (36%)	0.5904	
	SCN5A mutation	(patients)	16 (100%)	0	-	
	VT/VF during follow-up	(patients)	5 (31%)	23 (19%)	0.3197	
ECG parameters	Spontaneous type 1 ECG		(patients)	13 (81%)	96 (78%)	1.0000
	PQ interval (ms)	II	Pre SCB	195 ± 29	180 ± 27	0.0247
			Post SCB	259 ± 39	231 ± 36	0.0037
	QRS width (ms)	V1	Pre SCB	113 ± 24	107 ± 14	0.8274
			Post SCB	163 ± 42	132 ± 20	0.0012
		V2	Pre SCB	114 ± 23	108 ± 15	0.4853
			Post SCB	167 ± 43	135 ± 20	0.0015
	ST level (mV)	V1	Pre SCB	0.182 ± 0.103	0.161 ± 0.104	0.7426
			Post SCB	0.210 ± 0.131	0.287 ± 0.177	0.0905
		V2	Pre SCB	0.291 ± 0.152	0.290 ± 0.177	0.7024
			Post SCB	0.482 ± 0.290	0.593 ± 0.276	0.1359
	QTc interval (ms)	V5	Pre SCB	386 ± 30	392 ± 30	0.6927
			Post SCB	451 ± 51	432 ± 34	0.1757
	Drug-induced VA (n)	overall		4 (25%)	15 (12%)	0.2386
		PVCs		1 (6%)	9 (7%)	1.0000
VTs			3 (19%)	6 (5%)	0.0713	

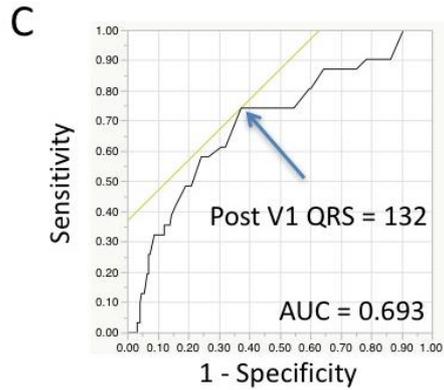
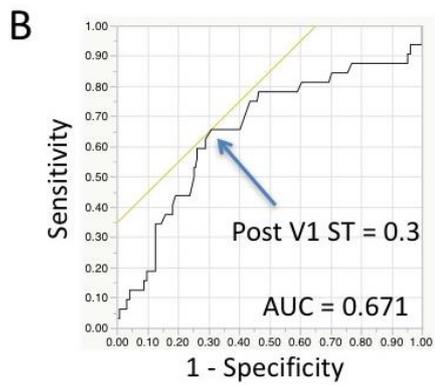
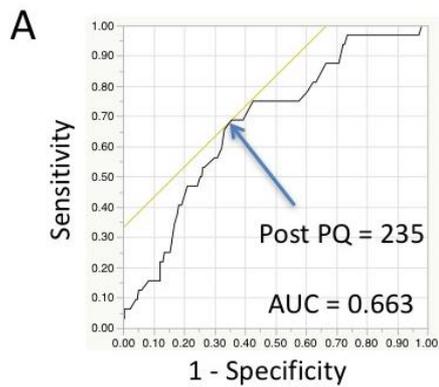
* *p* value: comparison of ECG parameters before and after the SCB test.

SCB: sodium channel blocker, SD: sudden death, VTA: ventricular tachyarrhythmia, VT/VF: ventricular tachycardia/ventricular fibrillation.

Figure S1. Receiver operating curves (ROC) for fatal arrhythmic events

during follow-up. ROC curves of PQ interval (A), ST level in lead V1 (B) and

QRS interval in lead V1 (C) after administration of pilsicainide.



Post PQ (ms)	Sensitivity (%)	Specificity (%)
230	74	57
235	65	66
240	55	70

Post V1ST (mV)	Sensitivity (%)	Specificity (%)
0.29	68	66
0.3	68	69
0.32	61	72

Post V1QRS (ms)	Sensitivity (%)	Specificity (%)
130	74	53
132	74	63
134	61	68