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) ≥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) unmask 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
documented VTA events have more advanced arrhythmogenic substrate on the epicardium.\textsuperscript{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.\textsuperscript{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: 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.

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

| Clinical parameters | Overall, n=245 | P Value* |
|---------------------|---------------|----------|
| 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) | 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   |       |

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.
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 (>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±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 χ² 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). 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).
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 pilsicainide administration 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 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).
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 VT/VF 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 detect VT/VF 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 (ΔPQ) and ST level (ΔST) 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 VT/VF 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: 15.6, CI, 4.3–56.1, P=0.0001) were also predictors of VT/VF events during follow-up.

**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.

**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.
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. The incidence of SCB-induced VTAs increased if the subjects of the study included subjects with spontaneous...
induced VTAs.

Without SCB-Induced VTAs

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                        | 113±22                          | 105±13                           | 0.0969   |
| Pre SCB                   | 145±36                          | 131±21                           | 0.0576   |
| Post SCB                  | 114±21                          | 106±13                           | 0.0429   |
| ST level (mV)             |                                 |                                  |          |
| V1                        | 200±0.132                       | 153±0.102                        | 0.0307   |
| Pre SCB                   | 385±0.219                       | 257±0.162                        | 0.0037   |
| Post SCB                  | 307±0.194                       | 293±0.157                        | 0.9613   |
| QTc interval (ms)         |                                 |                                  |          |
| V5                        | 387±29                          | 388±27                           | 0.8371   |
| Pre 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. 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. 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, and VTAs 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. This study included 35 asymptomatic patients with nonspor-taneous 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, 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 the patients have “definite” BrS 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. 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.
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. We could not determine sex risk of the SCB test in this study because we performed the test in only 5 female patients with non–type 1 ECG.
Table 4. Differences Between Patients With Spontaneous and Drug-Induced Type 1 ECG

| Clinical parameters | Spontaneous type 1 (n=181) | Drug-Induced type 1 (n=64) | P Value* |
|---------------------|-----------------------------|---------------------------|---------|
| 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

| ECG parameters | Spontaneous type 1 ECG | 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) | Pre SCB 108±14 | 101±14 | 0.0004 |
| Post SCB 134±23 | 128±22 | 0.0085 |
| V1              | Pre SCB 108±14 | 102±14 | 0.0011 |
| Post SCB 136±23 | 130±25 | 0.0041 |
| ST level (mV)   | 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) | 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* |
|----------|----------------------|-------------------|---------|
| 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

| ECG parameters | Spontaneous type 1 ECG | 0 | ... |
|----------------|------------------------|---|-----|
| 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) | Pre SCB 105±12 | 107±18 | 0.8629 |
| Post SCB 130±20 | 137±27 | 0.02 |
| V1              | Pre SCB 106±11 | 108±18 | 0.7396 |
| Post SCB 131±21 | 140±26 | 0.0026 |
| ST level (mV)   | 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) | 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.
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 Japanese studies, 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 6.** HR for Predicting VT/VF Events

| Clinical parameters | HR   | 95% CI          | P Value |
|---------------------|------|-----------------|---------|
| 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 |
|                       | ΔPQ      | 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 |
|           |   | ΔQRS     | 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 |
|    | ΔQRS     | 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 |
|          |   | ΔST      | 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 |
|    | ΔST      | 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 |
|              |   | ΔQT      | 1.01 | 0.99 to 1.02 | 0.1736 |

**Table 6. Continued**

| Drug-induced VT | HR   | 95% CI          | P Value |
|-----------------|------|-----------------|---------|
| 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; VT, ventricular tachyarrhythmia; VT/VF, ventricular tachycardia/ventricular fibrillation.

**Table 7.** Multivariable Analysis of Clinical and ECG Parameters for Predicting VT/A Events

| Baseline clinical parameters | HR   | 95% CI          | P Value |
|------------------------------|------|-----------------|---------|
| 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 ≥235 ms | 1.60 | 0.73 to 3.65 | 0.2399 |
| QRS interval ≥132 ms| 2.22 | 0.98 to 5.53 | 0.0559 |
| ST level ≥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; VT, 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.

| Clinical parameters | SCN5A (+) | SCN5A (-) | p value |
|---------------------|-----------|-----------|---------|
| 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%) | 0.2973  |
| VT/VF (patients)    | 2 (13%) | 8 (7%) | - |
| 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) | n = 16 | n = 123 | 0.0000 |
|----------------|----------------------------------|-------|--------|-------|
| 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.