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# Flecainide Therapy Reduces Exercise-Induced Ventricular Arrhythmias in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

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**Objectives** This study evaluated the efficacy and safety of flecainide in addition to conventional drug therapy in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).

**Background** CPVT is an inherited arrhythmia syndrome caused by gene mutations that destabilize cardiac ryanodine receptor $Ca^{2+}$ release channels. Sudden cardiac death is incompletely prevented by conventional drug therapy with β-blockers with or without $Ca^{2+}$ channel blockers. The antiarrhythmic agent flecainide directly targets the molecular defect in CPVT by inhibiting premature $Ca^{2+}$ release and triggered beats in vitro.

**Methods** We collected data from every consecutive genotype-positive CPVT patient started on flecainide at 8 international centers before December 2009. The primary outcome measure was the reduction of ventricular arrhythmias during exercise testing.

**Results** Thirty-three patients received flecainide because of exercise-induced ventricular arrhythmias despite conventional (for different reasons, not always optimal) therapy (median age 25 years; range 7 to 68 years; 73% female). Exercise tests comparing flecainide in addition to conventional therapy with conventional therapy alone were available for 29 patients. Twenty-two patients (76%) had either partial (n = 8) or complete (n = 14) suppression of exercise-induced ventricular arrhythmias with flecainide ($p < 0.001$). No patient experienced worsening of exercise-induced ventricular arrhythmias. The median daily flecainide dose in responders was 150 mg (range 100 to 300 mg). During a median follow-up of 20 months (range 12 to 40 months), 1 patient experienced implantable cardioverter-defibrillator shocks for polymorphic ventricular arrhythmias, which were associated with a low serum flecainide level. In 1 patient, flecainide successfully suppressed exercise-induced ventricular arrhythmias for 29 years.

**Conclusions** Flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy. (J Am Coll Cardiol 2011;57:2244–54) © 2011 by the American College of Cardiology Foundation

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a malignant inherited arrhythmia syndrome characterized by physical or emotional stress-induced bidirectional or polymorphic ventricular tachycardia (VT) in structurally

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normal hearts, with a high fatal event rate in untreated patients (1–3). Approximately 60% of CPVT patients have mutations in genes encoding the cardiac ryanodine receptor $Ca^{2+}$ release channel (RyR2) or cardiac calsequestrin (4–6), and these cause spontaneous RyR2 channel openings (7,8). The resulting increase in cytosolic $Ca^{2+}$ triggers delayed afterdepolarizations, ventricular premature beats (VPBs), and ventricular tachycardia, especially under conditions of β-adrenergic stimulation (9,10).

Hence, β-blockers are considered first-line therapy, but unfortunately they are not completely effective in preventing life-threatening arrhythmias (1–3,11–16). An implantable cardioverter-defibrillator (ICD) is often used in patients who continue to have ventricular arrhythmias despite β-blocker therapy. However, ICDs are not fully protective and can be proarrhythmic in CPVT patients because both appropriate and inappropriate ICD shocks can trigger catecholamine release, subsequently resulting in multiple shocks (arrhythmic storm), and death (17,18). Thus, additional therapy is desired for CPVT. Small case series show that left cardiac sympathetic denervation is effective in patients who are insufficiently protected by β-blocker therapy and/or experiencing too many ICD shocks (19–22).

Recently, we discovered that the antiarrhythmic agent flecainide directly blocks RyR2 channels, prevents RyR2-mediated premature $Ca^{2+}$ release, and suppresses triggered beats in myocytes isolated from mouse hearts lacking calsequestrin, an animal model of CPVT (23). This effect is not mediated by $Na^{+}$-channel block, the conventional mode of action thought to underlie flecainide activity, but rather can be attributed to open state block of RyR2 channels (that is, flecainide directly targets the molecular defect responsible for the arrhythmogenic $Ca^{2+}$ waves that trigger CPVT in vivo) (24). In preliminary work, flecainide also appeared to be effective in 2 highly symptomatic CPVT patients (23).

Here we collate the data from every CPVT patient started on flecainide at 8 international centers and report on the efficacy and safety of flecainide treatment in CPVT.

## Methods

**Participants and study design.** To better understand the efficacy and safety of flecainide in CPVT, we reviewed the chart of each consecutive CPVT patient in whom flecainide was started at 8 tertiary referral centers in the Netherlands, Canada, France, Israel, Japan, and the United States before December 2009. All patients had a clinical diagnosis of CPVT (based on exercise-induced bidirectional or polymorphic VT in the absence of structural cardiac disease) and a putative pathogenic mutation in the gene encoding RyR2 or cardiac calsequestrin. Determination of flecainide starting dose and dosing increases were made by the treating physician as part of specialized clinical care. Data collection and analysis were done retrospectively by chart review and were approved by the institutional review board at each participating institution.

**Abbreviations and Acronyms**

CPVT = catecholaminergic polymorphic ventricular tachycardia

ICD = implantable cardioverter-defibrillator

NSVT = nonsustained ventricular tachycardia

RyR2 = cardiac ryanodine receptor $Ca^{2+}$ release channel

VPB = ventricular premature beat

VT = ventricular tachycardia

**Primary and secondary outcome measures.** Couplets or VT during exercise are significantly associated with future arrhythmic events in CPVT (2). Because all patients were monitored by repeat exercise testing as part of routine clinical care, we used the reduction of ventricular arrhythmias during exercise testing as the primary outcome measure. The effect of flecainide was quantified by comparing the ventricular arrhythmia score (see later text) of the last exercise test on conventional therapy with the ventricular arrhythmia score of the first exercise test after a minimum of 5 days on the stable flecainide dose. Only patients on an unchanged or lower β-blocker dose during flecainide treatment were included in the primary analysis. Depending on the site, exercise testing was performed using a treadmill (standard or modified Bruce protocols) or bicycle ergometer.

Secondary outcome measures were the incidence of arrhythmic events (defined as syncope, aborted cardiac arrest, appropriate ICD shocks, and sudden cardiac death), assessment of well-being and side effects of flecainide, and monitoring of proarrhythmic effects of flecainide, in particular QRS duration during exercise and increase in the ventricular arrhythmia burden (25,26).

**Definitions of ventricular arrhythmia.** Exercise testing was analyzed and scored using the following pre-defined parameters (modified from Rosso et al. [27]): 1) ventricular arrhythmia score, defined by the worst ventricular arrhythmia (1, no or isolated VPBs; 2, bigeminal VPBs and/or frequent VPBs [>10 per min]; 3, couplet; and 4, nonsustained ventricular tachycardia [NSVT], ≥3 successive VPBs); 2) the presence of either of the parameters of the ventricular arrhythmia score or the presence of bidirectional VT (>3 successive VPBs with a beat-to-beat alternating right and left QRS axis); 3) sinus rate at the onset of ventricular arrhythmias, most often an isolated VPB; 4) maximum number of VPBs during a 10-s period; and 5)

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**Table 1** Baseline Characteristics and Flecainide Therapy Parameters

| Patient # | Sex | Mutation* | Age at First Symptom, yrs | Proband or Relative | Presenting Symptom | Age at Diagnosis, yrs | Aborted Cardiac Arrest | ICD | Age at Baseline, yrs | Drug Therapy at Baseline, mg (mg/kg body weight) | Indication for Starting Flecainide Treatment | Daily Starting/Stable Flecainide Dose, mg (mg/kg body weight)† | Follow-Up, months | Response to Flecainide Treatment | Side Effects of Flecainide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1‡ | F | A4091T | 5 | Proband | Seizure | 6 | Yes | Yes | 13 | Nadolol 160 (2.4), verapamil 180 (2.7)§ | NSVT (on Holter recordings) | 300 (4.5) | 25 | Complete | None |
| 2 | F | R2401H | 6 | Proband | Syncope | 6 | No | No | 7 | Nadolol 15 (0.9) | NSVT (on Holter recordings) | 96 (5.6)/120 (7.1) | 22 | None | None |
| 3‡ | M | CASQ2: 532+ 1G>A | NA | Relative | None | 3 | No | Yes | 12 | Metoprolol 125 (2.3), verapamil 120 (2.2)§ | NSVT (on ICD recordings) + frequent ICD shocks | 100 (1.9)/150 (2.8) | 28 | Complete | None |
| 4‡ | F | E4076K | 28 | Relative | Syncope | 31 | No | No | 37 | Metoprolol 100 (1.6) | Couplets + side effects | 100 (1.6)/150 (2.4) | 23 | Partial | None |
| 5 | F | S4124G | NA | Relative | None | 31 | No | No | 36 | Bisoprolol 5 (0.08), verapamil 240 (3.7)§ | NSVT + side effects | 100 (1.5)/150 (2.3) | 28 | Partial | None |
| 6 | F | S4124G | 45 | Proband | Syncope | 50 | No | No | 68 | Bisoprolol 2.5 (0.04) | NSVT + side effects | 75 (1.2)/150 (2.4) | 13 | Partial | Sinus arrest and dizziness |
| 7 | F | S4124G | 26 | Relative | Aborted cardiac arrest | 26 | Yes | No | 41 | None‖ | NSVT | 150 (2.2) | 22 | Partial | Dizziness |
| 8‡ | M | S4124G | 8 | Relative | Syncope | 8 | No | No | 10 | Metoprolol 50 (1.9) | Couplets | 50 (1.9)/100 (3.7) | 22 | Partial | None |
| 9‡ | M | E4187Q | NA | Proband | None (detected by cardiological examination after SCD of his son) | 47 | No | No | 53 | Metoprolol 200 (2.4) | NSVT + side effects | 150 (1.7) | 20 | Partial | None |
| 10‡ | M | E4187Q | NA | Relative | None | 19 | No | Yes | 25 | Metoprolol 200 (2.7) | NSVT | 150 (2.0) | 20 | None | None |
| 11‡ | F | E4187Q | NA | Relative | None | 14 | No | Yes | 20 | Metoprolol 150 (2.6) | NSVT | 100 (1.8) | 20 | Complete | None |
| 12‡ | M | E4187Q | NA | Relative | None | 11 | No | Yes | 17 | Metoprolol 100 (1.6) | NSVT | 100 (1.6)/300 (4.8) | 20 | Partial | None |
| 13 | F | E1724K | 13 | Relative | Syncope | 13 | No | No | 25 | Metoprolol 25 (0.4) | Couplets | 100 (1.3)¶# | NA# | NA# | Fatigue, dizziness, chest pain |
| 14 | F | E1724K | 9 | Proband | Syncope | 15 | No | No | 50 | Sotalol 160 (2.1) | Bigeminy/frequent VPBs + side effects | 100 (1.3) | 20 | None | None |
| 15‡ | M | R420W | NA | Relative | None | 38 | No | No | 49 | Metoprolol 100 (1.3) | Couplets | 150 (1.9)/300 (3.9) | 19 | Complete | None |
| 16‡ | M | R420W | NA | Relative | None | 12 | No | No | 16 | Metoprolol 100 (1.7) | NSVT | 100 (1.7) | 19 | Complete | None |
| 17 | F | Y4962C | NA | Relative | None | 41 | No | No | 45 | Atenolol 25 (0.4) | NSVT | 150 (2.5) | 12 | Complete | None |
| 18‡ | F | M2605V, A4510T, 14757-6_7CT>TA | NA | Proband | None (detected by exercise testing at pre-participation screening) | 40 | No | No | 40 | Metoprolol 100 (1.4) | Couplets | 200 (2.9) | 18 | Partial | None |

*Continued on next page*



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**Table 1 Continued**

| Patient # | Sex | Mutation* | Age at First Symptom, yrs | Proband or Relative | Presenting Symptom | Age at Diagnosis, yrs | Aborted Cardiac Arrest | ICD | Age at Baseline, yrs | Drug Therapy at Baseline, mg (mg/kg body weight) | Indication for Starting Flecainide Treatment | Daily Starting/Stable Flecainide Dose, mg (mg/kg body weight)† | Follow-Up, months | Response to Flecainide Treatment | Side Effects of Flecainide |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 19 | F | R420W | 33 | Proband | Syncope | 33 | No | Yes | 36 | Bisoprolol 5 (0.08) | Bigeminy/frequent VPBs | 100 (1.5) | 17 | Complete | None |
| 20 | M | R420W | NA | Relative | None | 11 | No | No | 12 | Atenolol 25 (0.7) | Couplets | 100 (2.6) | 23 | Complete | None |
| 21‡ | F | G3946S | 14 | Proband | Syncope | 15 | No | No | 34 | Nadolol 160 (2.7) | Couplets | 200 (3.3) | 18 | Complete | None |
| 22 | F | R420Q | 14 | Proband | Syncope | 15 | No | Yes | 20 | Bisoprolol 1.25 (0.03) | Couplets | 200 (4.0) | 17 | None | None |
| 23‡ | F | R2474G | 1 | Proband | Convulsion without fever | 11 | No | Yes | 18 | Atenolol 100 (2.1), verapamil 120 (2.6) | NSVT | 150 (3.2) | 20 | Complete | None |
| 24 | F | R420W | NA | Relative | None | 20 | Yes | No | 24 | Metoprolol 25 (0.4)# | Bigeminy/frequent VPBs + side effects | 100 (1.8) | 17 | Complete | None |
| 25 | F | E1724K | 10 | Proband | Syncope | 31 | No | No | 39 | Carvedilol 2.5 (0.05) | NSVT | 100 (2.2) | 14 | Partial | None |
| 26‡ | F | F2215L | 5 | Proband | Cardiac arrest | 10 | Yes | No | 24 | Propranolol 140 (2.8) | NSVT (on Holter recordings) + syncope + palpitations | 100 (2.0) | 13 | None | None |
| 27 | F | R4157H | 56 | Relative | Palpitations | 57 | No | Yes | 57 | Bisoprolol 5 (0.08)** | NSVT | 150 (2.3) | 31 | NA** | None |
| 28 | F | M3978I | 14 | Relative | Syncope | 15 | No | Yes | 25 | Nadolol 40 (0.7) | Frequent VPBs + syncope | 150 (2.5) | 31 | Complete | Nausea and dizziness |
| 29 | F | M3978I | 14 | Proband | Syncope | 14 | No | Yes | 26 | Bisoprolol 5 (0.06)†† | Bigeminy/frequent VPBs | 150 (3.1) | 32 | None | None |
| 30 | F | M3978I | 13 | Relative | Syncope | 32 | No | No | 45 | None‡‡ | Bigeminy/frequent VPBs | 150 (2.3) | NA§§ | Partial | Nausea and dizziness |
| 31 | F | M3978I | 13 | Relative | Syncope | 38 | No | No | 50 | Bisoprolol 5 (0.09) | VPBs + palpitations | 100 (1.8) | NA‖‖ | None | Nausea and dizziness |
| 32 | M | V4771I | 4 | Proband | Syncope with seizure | 18 | No | No | 18 | Sotalol 240 (3.2) | NSVT | 200 (2.7) | 29 yrs¶¶ | Complete | None |
| 33‡ | F | R2401H | 9 | Proband | Syncope | 9 | No | Yes | 17 | Nadolol 160 (2.5) | Syncope with VF and arrhythmic storm (recorded on ICD log) | 150 (2.3) | 40 | Complete | None |
| Total | F: 24 (73%) | *RyR2*: 32 (97%) | Median: 13 (range 1–56) | Probands: 15 (45%) | Symptoms: 21 (64%) | Median: 18 (range 3–57) | Yes: 4 (12%) | Yes: 12 (36%) | Median: 25 (range 7–68) | β-blocker: 31 (94%); $Ca^{2+}$ channel blocker: 4 (12%) | Severe ventricular arrhythmia: 26 (79%); symptoms: 5 (15%) | Median: 100 (range 50–300)/150 (range 100–300) | Median: 20 (range 12–40) | Complete: 14/31 (45%); partial: 10/31 (32%) | Yes: 6 (18%) |

*_RYR2_ mutations unless otherwise indicated. †Stable dose was identical to starting dose when only 1 dose is displayed. ‡Patients who were treated with a first-line β-blocker at an optimal dose (n = 15). §Verapamil was discontinued when flecainide was started. ‖This patient discontinued β-blocker therapy during 3 consecutive pregnancies, and thereafter agreed with her treating cardiologist to permanently discontinue β-blocker therapy and avoid exercise. ¶Flecainide was discontinued within a few days and before exercise testing on flecainide could be performed. #Metoprolol was discontinued and flecainide was started in this patient because of intolerable side effects. **This patient was not included in the primary analysis because the bisoprolol dose was also increased. ††This patient discontinued β-blocker therapy on her own initiative after flecainide treatment was started and before an exercise test on combined therapy could be performed. The ventricular arrhythmia score on flecainide monotherapy did not change compared with that on the baseline exercise test while taking a β-blocker. ‡‡This patient discontinued β-blocker therapy because of side effects. §§This patient discontinued flecainide and restarted β-blocker therapy on her own initiative. ‖‖This patient discontinued flecainide because of side effects after exercise testing while taking a β-blocker and flecainide was performed. ¶¶This patient was excluded from the follow-up calculation.

ICD = implantable cardioverter defibrillator; NA = not applicable; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death; VF = ventricular fibrillation; VPB = ventricular premature beat.

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ratio of VPBs to sinus beats during the 10-s period with the maximum number of VPBs.

Reaching a ventricular arrhythmia score of 1 was considered complete suppression of ventricular arrhythmias. Other ventricular arrhythmia score improvements were considered partial suppression.

**Statistical analysis.** Continuous data are presented as mean ± SD or median (range), and categorical variables as number (percentage). Related samples were compared using the paired Wilcoxon signed-rank test for continuous and ordinal variables and the McNemar test for dichotomous variables. Independent continuous variables were compared by means of the Mann-Whitney *U* test. A 2-tailed p value $<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS software package, version 15.0 (SPSS, Inc., Chicago, Illinois).

## Results

**Patient characteristics.** A total of 33 genotype-positive CPVT patients from 21 families were started on flecainide at 8 tertiary care centers (Table 1). All patients had persistent physical or emotional stress-induced ventricular arrhythmias documented by exercise testing, Holter recordings, or ICD interrogation and/or persistent symptoms of palpitations, syncope, aborted cardiac arrest, or appropriate ICD shocks, while taking β-blockers with or without $Ca^{2+}$-channel blockers. Twenty-four of the patients (73%) were female. The median age at the start of flecainide therapy was 25 years (range 7 to 68 years). Thirty-one patients (94%) were treated with β-blockers, and 4 (12%) of them also received $Ca^{2+}$-channel blockers (Table 1).

In 1 patient (Patient #13), flecainide was stopped because of side effects before exercise testing could be repeated; in another patient (Patient #27) the β-blocker dose was increased during flecainide treatment; and 2 patients (Patients #7 and #30) did not receive β-blocker therapy when flecainide was started (Table 1). In the remaining 29 patients, exercise tests on combination therapy of flecainide with conventional drugs at unchanged or lower doses were available for analysis. In 17 patients (59%), baseline exercise testing was performed <48 h before flecainide initiation.

**Flecainide therapy reduces exercise-induced ventricular arrhythmias.** Flecainide treatment improved the ventricular arrhythmia score in 22 patients (76%) ($p < 0.001$) (Fig. 1A). Fourteen patients (48%) had complete suppression of ventricular arrhythmias (including 7 patients without any VPBs), and 8 (28%) had partial suppression. None of the patients experienced significant (i.e., couplet or VT) worsening of the exercise-induced ventricular arrhythmia score.

Flecainide treatment also significantly improved all other predefined parameters of exercise-induced ventricular arrhythmia (Table 2). For example, patients receiving flecainide therapy achieved significantly higher heart rates before ventricular arrhythmias occurred. Independently, flecainide caused a significant reduction in maximum sinus rate during exercise, even though a higher mean workload was achieved. As expected (28), flecainide prolonged the PR interval (149 ± 21 ms vs. 160 ± 24 ms; $p = 0.003$), and the QRS duration (83 ± 9 ms vs. 89 ± 11 ms; $p = 0.005$), but did not change the QTc interval (399 ± 26 ms vs. 405 ± 19 ms; $p = 0.171$) at rest. These parameters remained within the normal range at rest and during peak exercise in all patients, except for a slightly prolonged resting PR interval (220 ms) in 1 patient (Patient #20).

We next assessed the reproducibility of exercise testing as a measure of the ventricular arrhythmia burden in CPVT. Although not available for all patients, a subset of patients underwent repeated exercise testing either at the same dose of conventional therapy (n = 14) or at the same flecainide dose (n = 16). In both cases, the ventricular arrhythmia score of the second exercise test was not statistically different from that on the first exercise test (Fig. 2). Similarly, all other predefined parameters of exercise-induced ventricular arrhythmia also did not change significantly (e.g., the maximum number of VPBs during a 10-s period was 5 ± 5 on the first exercise test at the stable flecainide dose and 6 ± 6 on the second exercise test at the same flecainide dose [$p = 0.556$]), suggesting that ventricular arrhythmia scores obtained from exercise testing are reproducible measures of drug efficacy in CPVT and that tachyphylaxis was not present.

We found that 14 of the 29 patients included in the primary analysis received drug therapy that could be considered suboptimal (i.e., an unusual β-blocker for CPVT [bisoprolol, carvedilol, or sotalol]) or a relatively low β-blocker dose (atenolol, metoprolol, or nadolol <1 mg/kg body weight daily) (2). These patients had either side effects on other β-blockers and/or a higher β-blocker dose, or nadolol was not available in their country. To assess whether flecainide was also effective in CPVT patients on optimal conventional therapy, we next analyzed the 15 patients who were treated with a first-line β-blocker at an optimal dose (Table 1). Flecainide significantly improved the ventricular arrhythmia score ($p = 0.003$) (Fig. 1B), and all other pre-defined arrhythmia parameters in this subgroup to a similar extent as in the primary analysis.

The ventricular arrhythmia score in the 2 patients (Patients #7 and #30) who did not receive β-blocker therapy when flecainide was started improved from NSVT to couplet and from NSVT to bigeminal VPBs and frequent VPBs, respectively.

**Flecainide dose in CPVT.** To estimate the optimal dosing of flecainide in CPVT, we analyzed the relationship between starting dose and VT suppression during the first exercise test on flecainide. Patients without suppression of exercise-induced ventricular arrhythmias on the starting flecainide dose received a significantly lower dose (113 ± 39 mg, n = 13; $p = 0.038$) compared with patients with either partial (142 ± 38 mg, n = 6) or complete ventricular arrhythmia suppression (150 ± 60 mg, n = 12). Eight

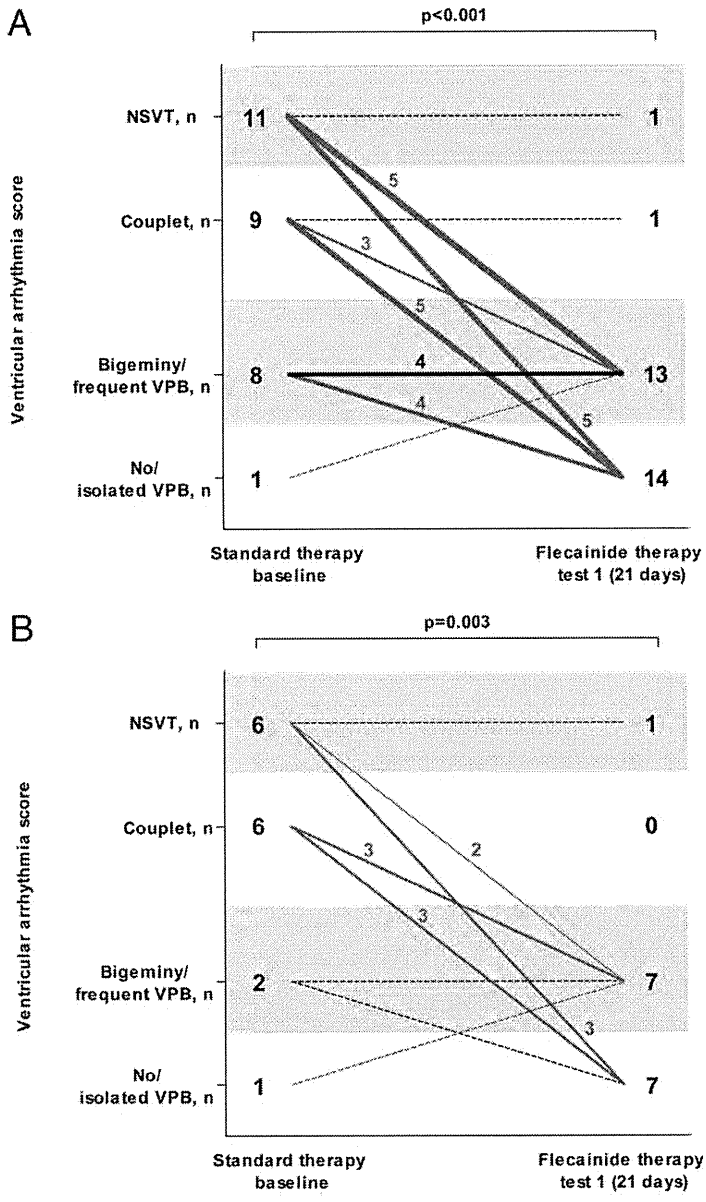


**Figure 1** **Ventricular Arrhythmia Score on Standard Therapy and on Flecainide**

Ventricular arrhythmia score per patient on the baseline exercise test on standard therapy and on the first exercise test on the final (stable) flecainide dose in the entire cohort (n = 29) **(A)** and in the patients who were treated with a first-line β-blocker at an optimal dose (n = 15) **(B)**. The number of patients in each ventricular arrhythmia category and change in ventricular arrhythmia category are shown. The **line thickness** indicates the number of patients, and a **dotted line** represents 1 patient. The median time interval between the 2 tests is shown. All exercise tests were performed on patients receiving an unchanged β-blocker dose. NSVT = nonsustained ventricular tachycardia; VPB = ventricular premature beats.

patients (24%) received an increased flecainide dose after the initial exercise test (Table 1). The dose increased from an average daily dose of 96 ± 28 mg to 178 ± 78 mg (range 100 to 300 mg), which resulted in a significant improvement in the ventricular arrhythmia score (Fig. 3).

**Clinical follow-up.** Three patients (Patients #13, #30, and #31) discontinued flecainide with <6 months of follow-up due to side effects. One patient (Patient #6) required a pacemaker because flecainide exacerbated pre-existing sinus node dysfunction. Flecainide was resumed after pacemaker implantation, and this patient was included in the study. In 2 patients (Patients #7 and #28), the stable flecainide dose was decreased because of dizziness. All other patients tolerated flecainide well without severe side effects. The β-blocker dose was decreased in 5 patients (Patients #4, #5, #6, #9, and #12) who had a partial suppression of ventricular arrhythmias on flecainide and experienced side effects of β-blocker therapy (in particular, fatigue) before flecainide

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**Table 2** Exercise Test Results of the Baseline Exercise Test on Standard Therapy and on the First Exercise Test on the Final (Stable) Flecainide Dose

| | Standard Therapy Baseline (n = 29) | First Exercise Test on Stable Flecainide Dose (n = 29) | p Value |
|---|---|---|---|
| Time after start flecainide, days | — | 21 (5–363) | — |
| Sinus rate at baseline, beats/min | 57 ± 10 | 59 ± 9 | 0.061 |
| Sinus rate at maximal exercise, beats/min | 145 ± 23 | 133 ± 18 | 0.002 |
| Maximum workload attained, METs | 11 ± 3 | 12 ± 4 | 0.042 |
| Sinus rate at onset of ventricular arrhythmias, beats/min | 113 ± 19 | 118 ± 19 | 0.046* |
| Maximum no. of VPBs during a 10-s period† | 12 ± 5 | 5 ± 5 | <0.001 |
| Ratio of VPBs to sinus beats during the 10-s period with the maximum no. of VPBs† | 1.2 ± 0.8 | 0.4 ± 0.4 | <0.001 |
| Isolated VPB | 29 (100) | 22 (76) | 0.016 |
| Bigeminal VPBs | 28 (97) | 13 (45) | <0.001 |
| Frequent VPBs (>10/min) | 27 (93) | 14 (48) | 0.001 |
| Couplet | 20 (69) | 2 (7) | <0.001 |
| Nonsustained ventricular tachycardia | 11 (38) | 1 (3) | 0.002 |
| Longest ventricular salvo, VPBs† | 5 (3–9) | 4 | — |
| Bidirectional NSVT | 4 (36) | — | — |

Data are mean ± SD, median (range), or n (%). *Only the 22 patients who still had ventricular arrhythmias on the first exercise test at the stable flecainide dose were included in this analysis. †Data were available for 28 patients (not available for Patient #32).
MET = metabolic equivalent; NSVT = nonsustained ventricular tachycardia; VPB = ventricular premature beat.

was started. One patient (Patient #29) refused to take β-blockers during follow-up, with no worsening of exercise-induced ventricular arrhythmias on flecainide monotherapy.

Thus, 30 of 33 patients (91%) continued to receive flecainide and were included in the further analysis of the incidence of arrhythmic events. During a median follow-up of 20 months (range 12 to 40 months, excluding Patient #32), VT recurred in only 1 patient (Patient #1) who experienced several appropriate ICD shocks for polymorphic VT after 8 months of flecainide treatment. Her serum flecainide level was low (0.34 μg/ml) at the time of the event compared with levels obtained previously (0.75 to 0.82 μg/ml), suggesting noncompliance. She was hospitalized for 48 h, nadolol and flecainide were resumed at their previous doses, and no further ventricular arrhythmias occurred during a further follow-up of 17 months. The other 29 patients remained free of arrhythmic events during follow-up. The longest follow-up of 29 years was achieved in Patient #32, who presented with exercise-induced VT in 1981. After unsuccessful trials of multiple antiarrhythmic drugs (including mexilitine, amiodarone, propranolol, sotalol, and $Ca^{2+}$-channel blockers), flecainide (200 mg/day) was added to sotalol (160 mg/day), which resulted in complete suppression of ventricular arrhythmia during exercise testing. In 2008, an exercise test 48 h after stopping flecainide and sotalol showed NSVT. After restarting the combined therapy, a subsequent exercise test only showed isolated VPBs, but no VT. Subsequent genotyping revealed a mutation in the gene encoding RyR2. In Patient #33, flecainide 150 mg/day was started in 2007 because of 2 episodes of syncope with ventricular fibrillation on the ICD interrogation despite nadolol 240 mg/day. Exercise testing showed complete suppression of ventricular arrhythmias, and she has been free of arrhythmic events on flecainide for 40 months.

## Discussion

**Main findings.** Our study demonstrates that flecainide reduces or prevents exercise-induced ventricular arrhythmias in the majority of CPVT patients receiving conventional drug therapy. These findings are important because several studies have demonstrated a significant failure rate of current drug therapy (1,3,11–16), including potentially fatal arrhythmic events in 11% of CPVT patients over an 8-year period (2). Based on our clinical experience reported here, flecainide in addition to β-blocker therapy should be considered for CPVT patients who otherwise have few alternative therapeutic options. The optimal dose appears to be between 150 and 200 mg/day (range 100 to 300 mg/day). Daily doses <100 mg were associated with a lack of therapeutic response.

**Rationale for use of flecainide.** CPVT is caused by mutations in the genes encoding RyR2 and cardiac calsequestrin (4,5), 2 proteins that control $Ca^{2+}$ release from the sarcoplasmic reticulum. As a result of the mutations, $Ca^{2+}$ is released prematurely and excessively into the cytosol under conditions of catecholaminergic stimulation, generating repetitive spontaneous $Ca^{2+}$ waves (9,29). The increase in intracellular $Ca^{2+}$ in turn activates the electrogenic $Na^+/Ca^{2+}$ exchanger, which produces a transient inward current ($I_{Ti}$). $I_{Ti}$ generates delayed afterdepolarizations, which can lead to triggered activity, and the initiation of ventricular arrhythmias (30). Flecainide directly targets the molecular defect in CPVT by inhibiting RyR2 channels and preventing arrhythmogenic $Ca^{2+}$ waves (23,24). Flecain-

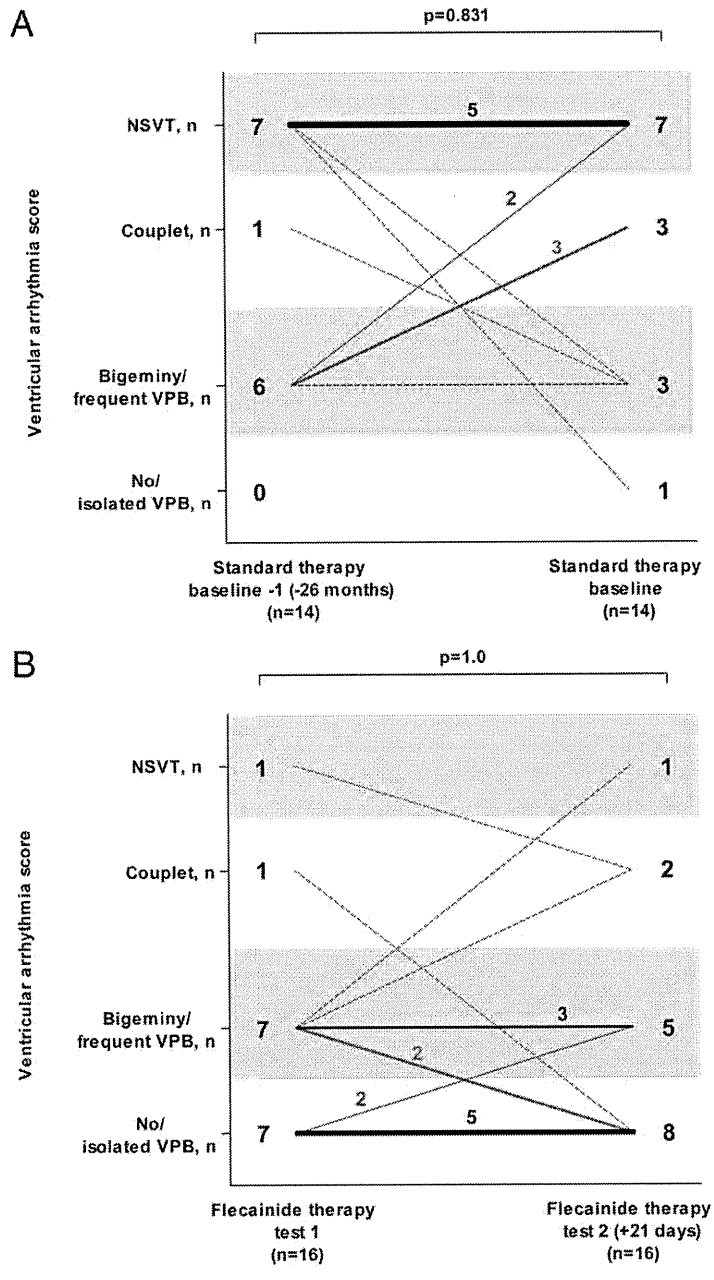


**Figure 2** **Reproducibility of Ventricular Arrhythmia Score on Exercise Testing**

Ventricular arrhythmia score per patient on the baseline exercise test and on the previous exercise test at the same standard therapy dose **(A)** and on the first and second exercise tests at the final (stable) flecainide dose **(B)**. The number of patients in each ventricular arrhythmia category and change of ventricular arrhythmia category are shown. The **line thickness** indicates the number of patients, and a **dotted line** represents 1 patient. The median time interval between the 2 tests is shown. The standard therapy exercise tests were performed on patients receiving the same β-blocker dose with or without $Ca^{2+}$-channel blocker. All exercise tests on patients receiving flecainide were at the same stable flecainide dose in combination with an unchanged or lower β-blocker dose. The sinus rates at maximal exercise on the first and second exercise tests on flecainide were not significantly different (140 ± 19 vs. 144 ± 20; p = 0.245). However, the 2 patients with a ventricular arrhythmia score of 4 and 3 on the second exercise test did reach a significantly higher maximum sinus rate compared with the first exercise test (increase of 32 and 19 beats/min, respectively). Abbreviations as in Figure 1.

ide's $Na^{+}$-channel blockade further reduces the rate of triggered beats (23,24). This dual action could explain why flecainide is so effective in severe CPVT and provides a rationale for combination therapy with β-blockers.

RyR2-mediated sarcoplasmic reticulum $Ca^{2+}$ release importantly regulates the beating rate of sinoatrial nodal cells (31), especially in response to catecholamines (32), and flecainide reduces the rate of spontaneous sarcoplasmic

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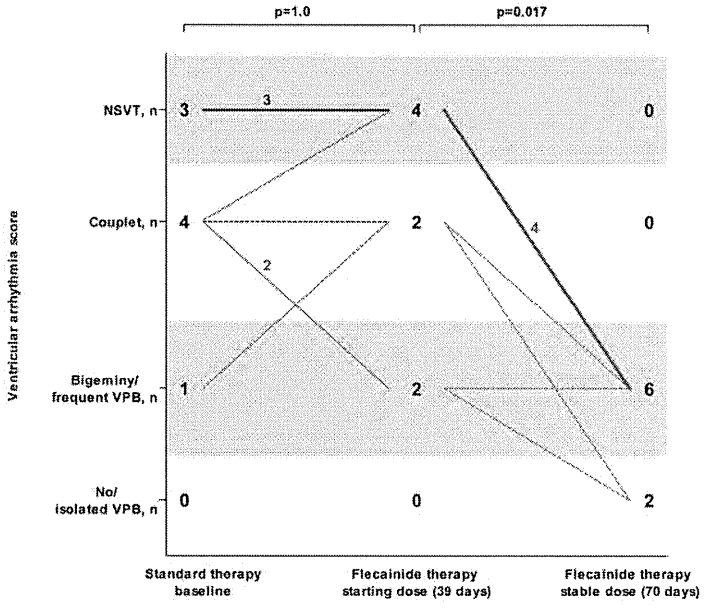


**Figure 3** **Dose Dependence of Flecainide in 8 CPVT Patients Who Had an Increase in Flecainide Dose**

The number of patients in each ventricular arrhythmia category and change in ventricular arrhythmia category on the last exercise test at the flecainide starting dose (96 ± 28 mg; range 50 to 150 mg) and on the first exercise test at the final (stable) flecainide dose (178 ± 78 mg; range 100 to 300 mg) is shown. The **line thickness** indicates the number of patients, and a **dotted line** represents 1 patient. The median time interval from the start of flecainide therapy is shown. All exercise tests were performed with the patients receiving an unchanged β-blocker dose. Abbreviations as in Figure 1.

reticulum $Ca^{2+}$ release in myocytes (24). This mechanism may explain why maximum hearts rates were significantly lower in flecainide-treated patients even though workloads were higher compared with baseline exercise testing (Table 2). The reduction in sinus rate during exercise may further contribute to flecainide's efficacy in CPVT.

**Clinical implications.** Given the high fatality rate of untreated CPVT patients (1,2), adequate treatment is mandatory and potentially life-saving. β-blockers are considered first-line therapy. In the largest published series of patients with CPVT, the risk of cardiac arrest (defined as aborted cardiac arrest, appropriate ICD shocks, and sudden cardiac death), despite β-blocker therapy during a mean follow-up period of 8 years, was 11% (2). Others have reported very diverse fatal or near-fatal event rates despite β-blocker therapy (1,3,11–16), although the highest event rates may be explained by the predominance of (symptomatic) probands and underdosing of β-blockers. An ICD was recommended for CPVT patients who were survivors of cardiac arrest, or when syncope or sustained VT persisted despite maximum tolerable β-blockade (33). Yet, ICDs have a potentially harmful effect in CPVT patients (17,18). Moreover, many CPVT patients are children, in whom ICD implantation can lead to significant complications (34). Thus, to avoid ICD implantation and prevent ICD shocks in patients with ICDs, controlling ventricular arrhythmias is of great clinical importance. Alternative therapies are needed for CPVT patients.

Left cardiac sympathetic denervation is an effective alternative when symptoms persist despite β-blockade, but requires surgery, is not universally available, and has only been tested in small cohorts (19–22). The use of $Ca^{2+}$-channel blockers in addition to β-blockade has been reported to decrease ventricular ectopy in CPVT patients with continuous symptoms and/or exercise-induced ventricular arrhythmias (12,27,35), but is not effective in all patients (27,35,36). From the original 6 patients treated with verapamil and β-blockers after failure of β-blockers alone, reported by Rosso et al. (27) in 2007, 3 had clinically significant ventricular arrhythmias during 37 ± 6 months of follow-up (36). Other pharmacological agents, including $Na^{+}$-channel blockers, amiodarone, and magnesium, lack of efficacy in CPVT patients (1,12).

In this analysis of all consecutive patients started on flecainide at 8 international centers, adding flecainide to standard therapy was effective in further reducing exercise-induced VT and preventing arrhythmic events CPVT patients. To suppress CPVT, adequate dosing of flecainide seems critical. An increased dose may be effective when the initial dose of flecainide fails to suppress VT. Based on these results, flecainide could be added to β-blocker therapy when symptoms or either spontaneous or exercise-induced ventricular arrhythmias persist despite β-blocker.

In our young patient population with no structural heart disease, the proarrhythmic effect of flecainide as documented in patients with ischemia and impaired left ventric-

ular function (37) may not be applicable. Consistent with this hypothesis, flecainide did not cause arrhythmic events during a median follow-up of 20 months, which is longer than the mean follow-up of 10 months in the CAST (Cardiac Arrhythmia Suppression Trial). The only arrhythmic event was associated with low flecainide serum levels, suggesting that the event was due to the underdosing and not toxicity.

**Study limitations.** This study reports on our experience of using flecainide in a clinical setting. The number of patients is relatively small because CPVT is a rare condition and only patients without other treatment alternatives were started on flecainide. However, it is the largest evaluation of a new therapeutic strategy in CPVT patients refractory to current drug therapy, with a median of 20 months follow-up. One patient has received flecainide for 29 years with continuous VT suppression on unchanged doses, and another severely symptomatic patient has been free of arrhythmic events on flecainide for 40 months. Nevertheless, long-term follow-up in more patients would further support the clinical utility of flecainide in CPVT.

Another potential limitation is that we only quantified the effect of flecainide on exercise-induced ventricular arrhythmias, which may not accurately predict fatal arrhythmic events. However, exercise testing is clinically used to guide therapy in CPVT. In a previous study including 70 CPVT patients, exercise-induced couplets or more successive VPBs were significantly associated with future arrhythmic events (sensitivity, 0.62; specificity, 0.67) (2).

Furthermore, we cannot exclude potential bias introduced by the variability of exercise test results on unchanged treatment, as illustrated in Figure 2. Finally, in 14 patients, conventional therapy may be considered suboptimal because they received an unusual β-blocker for CPVT or a low β-blocker dose for reasons previously outlined. However, flecainide was equally effective in the subgroup of CPVT patients who were treated with a first-choice β-blocker at an adequate dose (Fig. 1B).

## Conclusions

Our results suggest that flecainide is a safe and effective therapy to reduce ventricular arrhythmias in the majority of CPVT patients who have exercise-induced ventricular arrhythmias despite conventional therapy.

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**Key Words:** antiarrhythmia agents ▪ catecholaminergic polymorphic ventricular tachycardia ▪ ventricular arrhythmia.

# High prevalence of early repolarization in short QT syndrome

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**BACKGROUND** Short QT syndrome (SQTS) is characterized by an abnormally short QT interval and sudden death. Due to the limited number of cases, the characteristics of SQTS are not well understood. It has been reported recently that early repolarization is associated with idiopathic ventricular fibrillation and the QT interval is short in patients with early repolarization.

**OBJECTIVE** The purpose of this study was to study the association between early repolarization and arrhythmic events in SQTS.

**METHODS** The study consisted of three cohorts: SQTS cohort (N = 37), control cohort with short QT interval and no arrhythmic events (N = 44), and control cohort with normal QT interval (N = 185). ECG parameters were compared among the study cohorts.

**RESULTS** Heart rate, PR interval, and QRS duration were similar among the three study cohorts. Early repolarization was more common in the SQTS cohort (65%) than in the short QT control cohort (30%) and the normal QT control cohort (10%). Duration from T-wave peak to T-wave end was longer in the SQTS cohort than in the short QT control cohort, although QT and corrected QT intervals were similar. In the SQTS cohort, there were more males among patients with arrhythmic events than in those with a family history but without arrhythmic events. In multivariate models, early repolarization was associated with arrhythmic events in the SQTS cohort. ECG parameters including QT and QTc intervals were not associated with arrhythmic events in the SQTS cohort.

**CONCLUSION** There is a high prevalence of early repolarization in patients with SQTS. Early repolarization may be useful in identifying risk of cardiac events in SQTS.

**KEYWORDS** Arrhythmia; Electrocardiogram; QT interval; Repolarization; Sudden death

**ABBREVIATIONS** **QTc** = corrected QT interval; **SQTS** = short QT syndrome

(Heart Rhythm 2010;7:647–652) 

## Introduction

The short QT syndrome (SQTS) is characterized by an abnormally short QT interval and increased risk of ventricular fibrillation and sudden death.[1,2] Similar to other arrhythmia syndromes, such as long QT syndrome and Brugada syndrome,[3] SQTS is a genetically heterogeneous disease, and, to date, five responsible genes encoding different ion channels have been identified.[3–7] Some inherited arrhythmia syndromes may share genetic backgrounds that result in overlapping arrhythmia phenotypes.[3]

Although early repolarization is generally considered benign,[8] it has been reported recently that early repolarization is associated with increased risk for sudden cardiac death in patients with idiopathic ventricular fibrillation.[9–12] Haissaguerre et al[9] reported that, among patients with idiopathic ventricular fibrillation, the QT interval was shorter in patients with early repolarization than in those without, suggesting an association between early repolarization and QT interval shortening. Evidence that mutations in calcium channel genes are associated with Brugada-type ST-segment elevation and abnormally short QT intervals further suggests a relationship between early phase repolarization abnormalities and short QT interval.[4] Here we report on our

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study of the prevalence of early repolarization and its association with arrhythmic events in SQTS.

## Methods

This cooperative study consisted of three cohorts. (1) *SQTS cohort* included patients with SQTS referred to our institutions and patients with SQTS from previous reports. The diagnosis of SQTS was made if a patient with a short QT interval [corrected QT interval (QTc) by Bazett formula ≤330 ms] had an arrhythmic event including documented ventricular fibrillation, resuscitated sudden cardiac death, and syncope and/or had a family history of SQTS, or if a patient with a short QT interval (QTc ≤360 ms) had mutations in ion channel genes responsible for SQTS.[3,13] We searched in the electronic databases PubMed, EMBASE, and Cochrane for all published studies that examined patients with SQTS. The search was limited to the end of June 2009. Published studies were considered eligible if they included clinical characteristics of the patients and ECGs. All ECGs from patients reported in the literature were reanalyzed. Electrophysiologic study was performed in patients with SQTS based on the indication of each institution. (2) *Control cohort with short QT interval* (QTc ≤330 ms) *and no arrhythmic events* was selected from among 86,068 consecutive ECGs stored on the ECG database at Niigata University Medical and Dental Hospital from May 7, 2003 to July 2, 2009. Subjects who did not have arrhythmic events or cardiovascular disease and were not taking any medication were included in this cohort. (3) *Control cohort with normal QT interval* was also selected from the ECG database. This cohort consisted of subjects who were matched to the SQTS cohort for gender and age. Subjects who had normal QT interval (360–440 ms) and did not have cardiovascular disease or were not taking any medication were included in this cohort. Subjects with Brugada-type ST-segment elevation were excluded from all study cohorts.[3,9]

QT intervals were measured on lead $V_2$ with the tangent methods for determination of $QT_{end}$ using a semi-automated digitizing program with electronic calipers by an experienced observer blinded to the clinical details of all subjects included in this study.[14,15] Early repolarization was defined as elevation of the J point noted as either as QRS slurring or notching ≥0.1 mV in more than two leads.[9]

Differences in parameters were analyzed using multivariable logistic regression models when SQTS cohort and control cohort with short QT interval were compared and analyzed using conditional logistic regression models when SQTS cohort and control cohort with normal QT interval were compared. All statistical analyses were performed with SPSS (version 12.0, SPSS, Inc., Chicago, IL, USA). Two-sided $P < .05$ was considered significant. Values are expressed as mean ± SD. The study protocol was approved by the Ethics Committee of Niigata University School of Medicine. To determine interobserver variability, a second observer made independent blinded QT interval determinations of all study subjects with short QT interval.

## Results

Thirty-seven patients with SQTS were identified: 12 from our institutions and 25 reported in the literature,[2,5,6,14,16–25] Forty-four control subjects with short QT interval and 185 control subjects with normal QT interval also were identified (Table 1). The SQTS cohort consisted of 25 (68%) patients with symptoms, including 14 with cardiac arrest (3 sudden death, 11 resuscitated) and 11 with syncope. Genetic screening identified mutations in ion channels in 7 (41%) of 17 probands who were genetically screened (2 *KCNQ1*, 4 *KCNH2*, 1 *KCNJ2*). Among patients in our institutions and those reported in the literature, there was no difference with regard to gender, age, prevalence of family history, QT or QTc interval, or inducibility of ventricular tachyarrhythmia by electrical programmed stimulation.

Heart rate, PR interval, and QRS duration in the SQTS cohort were not different among patients in either the short QT control cohort or the normal QT control cohort (Table 1). QT and corrected QT intervals were shorter in the SQTS and short QT control cohorts than in the normal QT control cohort. Early repolarization occurred in 24 (65%) patients with SQTS (Figure 1). Interobserver variability between two investigators was 8.6 ms (95% confidence interval −0.5 to 17.7 ms) for QT interval and 9.0

**Table 1** ECG parameters of study cohorts

| | Patients with SQTS (N = 37) | Subjects with short QTc (N = 44) | Versus subjects with short QTc* | | Subjects with normal QTc† (N = 185) | Versus subjects with normal QTc | |
|---|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *P* value | | OR (95% CI) | *P* value |
| Male gender [N (%)] | 27 (73) | 34 (77) | 2.84 (0.72–11.2) | .14 | 135 (73) | — | — |
| Age (years) | 30 ± 19 | 47 ± 23 | 1.05 (1.02–1.08) | .001 | 30 ± 19 | — | — |
| Heart rate (bpm) | 69 ± 393 | 65 ± 398 | 1.00 (1.00–1.01) | .3 | 70 ± 327 | 1.00 (1.00–1.00) | 0.70 |
| PR interval (ms) | 138 ± 19 | 153 ± 38 | 1.01 (0.99–1.03) | .54 | 143 ± 24 | 0.99 (0.97–1.01) | 0.18 |
| QRS interval (ms) | 86 ± 7 | 84 ± 8 | 0.97 (0.91–1.04) | .38 | 85 ± 7 | 1.01 (0.96–1.06) | 0.74 |
| QT interval (ms) | 286 ± 36 | 286 ± 15 | 0.99 (0.97–1.01) | .28 | 367 ± 36 | 0.97 (0.96–0.98) | <0.001 |
| QTc (ms) | 308 ± 29 | 299 ± 21 | 0.98 (0.96–1.00) | .06 | 399 ± 24 | 0.97 (0.97–0.98) | <0.001 |

CI = confidence interval; OR = odds ratio; QTc = corrected QT interval; SQTS = short QT syndrome.

*Models were adjusted for gender and age.

†Gender and age were matched between patients with SQTS and subjects with normal QT interval.

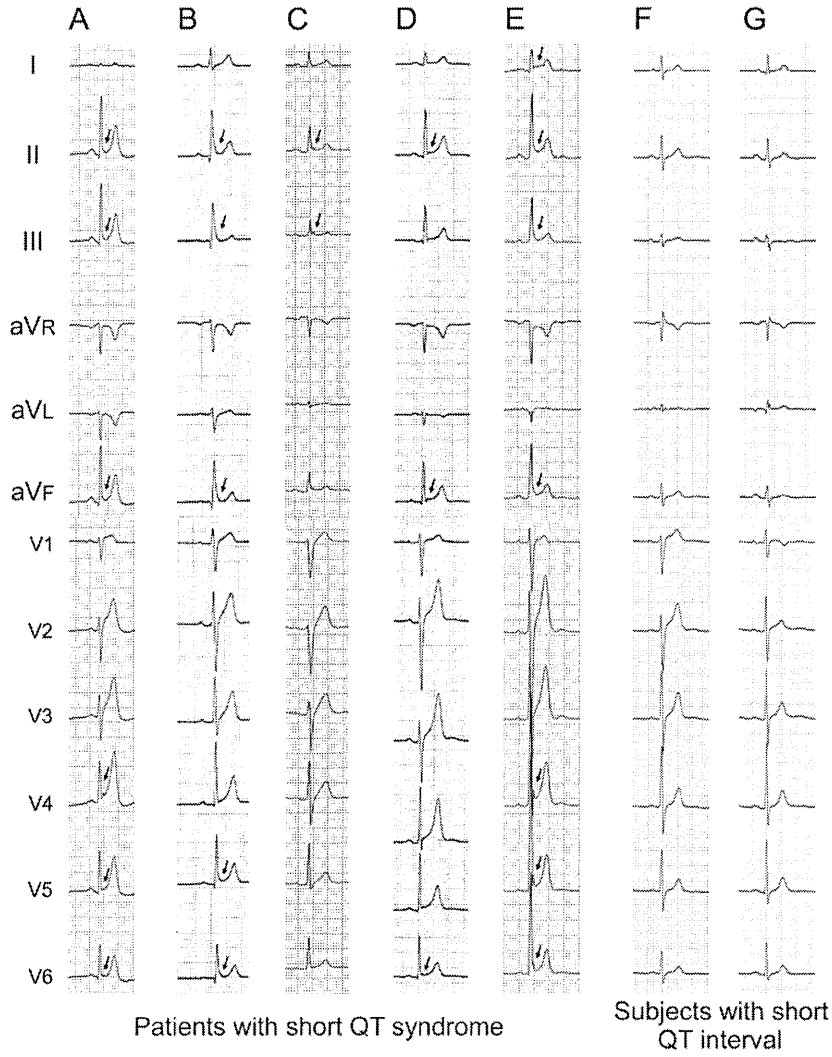


**Figure 1** Early repolarization in short QT syndrome. ECGs were recorded from patients with short QT syndrome (**A:** 61-year-old woman; **B:** 30-year-old man; **C:** 38-year-old man; **D:** 31-year-old man; **E:** 22-year-old man) and control subjects with a short QT interval (**F:** 23-year-old man; **G:** 44-year-old woman). In each patient with short QT syndrome, early repolarization was evident in the inferolateral leads (*arrows*).

ms (95% confidence interval −0.6 to 18.7 ms) for QTc interval. The frequency of early repolarization was not different between patients in our institutions and those reported in the literature. Early repolarization was present in the inferior leads (II, III, aVF) in 9 patients, in the lateral leads (I, aVL, $V_4$–$V_6$) in 6 patients, and in both the inferior and lateral leads in 9 patients. Of 10 probands with early repolarization genetically screened, mutations were identified in 3 patients (1 *KCNQ1*, 2 *KCNH2*). Early repolarization was more common in the SQTS cohort than in the short QT control and normal QT control cohorts (Figure 2).

The association of early repolarization with arrhythmic events then was studied in patients with SQTS. In the SQTS cohort, there were more males among patients with arrhythmic events than among those with a family history but without arrhythmic events (Table 2). In multivariate models adjusted for gender and age, early repolarization was associated with arrhythmic events, although ECG parameters including QT and QTc intervals were not associated with arrhythmic events. Early repolarization remained associated with arrhythmic events after adjustment for age, gender, and QTc interval ($P$ = .001). Electrophysiologic study performed in 18 patients with SQTS revealed no difference in inducibility of ventricular tachyarrhythmia between patients with arrhythmic events (73%) and those without arrhythmic events (71%).

QT interval parameters were compared between SQTS and short QT control cohorts because some of the parameters recently have been associated with SQTS.[26] Interval from T-wave peak to T-wave end ($T_{peak}$ to $T_{end}$) was longer in the SQTS cohort than in the short QT control cohort even after heart rate correction using the Bazett formula, whereas QT interval, QTc interval, and interval from Q-wave to T-wave peak ($QT_{peak}$) were not different between the two cohorts (Table 3). Ratio of $T_{peak}$ to $T_{end}$ per QT was larger in the SQTS cohort than in the short QT control cohort.

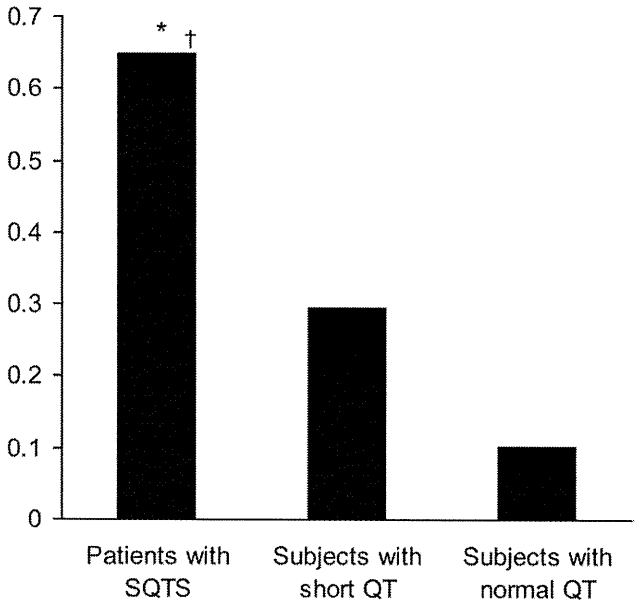


**Figure 2** Frequency of early repolarization. Odds ratios (95% confidence intervals) for early repolarization in patients with short QT syndrome (SQTS) were 5.64 (1.97–16.15) and 16.58 (7.2–38.21) versus subjects with short QT interval and those with normal QT interval, respectively. *$P$ = .001 vs subjects with short QT interval. †$P$ <.001 vs subjects with normal QT interval.

## Discussion

SQTS is a recently discovered, very rare disease with an increased risk of sudden death.[2] Due to the limited number of cases, the characteristics of SQTS are not well understood. Therefore, we conducted a cooperative analysis of ECGs from patients with SQTS in our institutions and those reported in the literature and found that early repolarization is common in SQTS.

Early repolarization is a common ECG finding. It is present in 1% to 13% of the general population and usually is considered as a normal variant due to its benign long-term prognosis.[8,11,27–29] However, increasing evidence suggests that early repolarization is associated with arrhythmia.[9,27,30–34] Since 1985, we and other investigators have reported an association between early repolarization (or late depolarization) and sudden cardiac death.[30–32] A multicenter study including our institution recently showed that early repolarization is present in one third of patients with idiopathic ventricular fibrillation.[9] Early repolarization is associated with increased risk of sudden cardiac arrest in idiopathic ventricular fibrillation, and the amplitude of early repolarization increases before development of arrhythmic events.[9,10] In Brugada syndrome, which is characterized by J-wave and ST-segment elevation in the right precordial leads on ECG and sudden cardiac death,[3] early repolarization in the inferolateral leads is not uncommon and is associated with arrhythmic events,[34] although another report has shown negative results.[33] In our study, early repolarization in the inferolateral leads was frequently found in SQTS and, more importantly, was associated with arrhythmic events in SQTS. In addition to arrhythmia syndromes unassociated with structural heart disease, a high frequency of early repolarization in arrhythmogenic right ventricular dysplasia/cardiomyopathy has been reported.[27]

It has been suggested that SQTS and idiopathic ventricular fibrillation share clinical characteristics.[23] Short QT interval is frequently found in idiopathic ventricular fibrillation,[23] and QT interval is relatively short in patients with idiopathic ventricular fibrillation who have early repolarization.[9] Spontaneous and inducible ventricular fibrillation can be initiated by short-coupled premature ventricular beat in SQTS and idiopathic ventricular fibrillation.[21,35,36] The efficacy of isoproterenol and quinidine has been reported for both arrhythmia syndromes,[21,37] although the arrhythmogenic effects of isoproterenol in an experimental model of SQTS have been reported.[38] Our study showing an association of early repolarization with SQTS further supports the presence of common arrhythmogenic substrates in SQTS and idiopathic ventricular fibrillation.

A precise mechanism for ventricular fibrillation in SQTS is not known, but characteristic ECG abnormalities may reflect arrhythmogenicity. A prior study showed that the interval from T-wave peak to T-wave end is relatively long in SQTS, and our study replicated the results.[26] T-wave peak to T-wave end interval is considered to reflect transmural dispersion of repolarization, and relative prolongation of the interval in SQTS may indicate a high vulnerability to ventricular fibrillation.[39] An experimental model of SQTS

**Table 2** Characteristics of SQTS patients with and those without arrhythmic events

| | Patients with arrhythmic events (N = 25) | Patients without arrhythmic events (N = 12) | OR (95% CI) | $P$ value |
|---|---|---|---|---|
| Male gender [N (%)] | 21 (84) | 6 (50) | 10.44 (0.85–127.48) | .07 |
| Age (years) | 30 ± 19 | 23 ± 18 | 1.05 (0.99–1.12) | .13 |
| Heart rate (bpm) | 69 ± 393 | 76 ± 473 | 1.00 (1.00–1.01) | .38 |
| PR interval (ms) | 138 ± 19 | 134 ± 18 | 0.99 (0.95–1.04) | .84 |
| QRS interval (ms) | 86 ± 7 | 85 ± 10 | 0.93 (0.82–1.07) | .31 |
| QT interval (ms) | 286 ± 36 | 271 ± 40 | 1.00 (0.97–1.03) | .75 |
| QTc (ms) | 308 ± 29 | 306 ± 33 | 0.98 (0.94–1.02) | .33 |
| Early repolarization [N (%)] | 22 (88) | 2 (17) | 46.53 (4.52–478.79) | .001 |

CI = confidence interval; OR = odds ratio; QTc = corrected QT interval; SQTS = short QT syndrome.
Models were adjusted for gender and age.

**Table 3** ECG parameters for study cohorts with short QT interval

| | Patients with SQTS | Subjects with short QTc | OR (95% CI) | *P* value |
|---|---|---|---|---|
| $QT_{peak}$ (ms) | 211 ± 37 | 222 ± 19 | 0.99 (0.98–1.01) | .37 |
| Corrected $QT_{peak}$ | 226 ± 32 | 234 ± 24 | 0.99 (0.98–1.01) | .56 |
| $T_{peak}$ to $T_{end}$ (ms) | 81 ± 21 | 67 ± 13 | 1.08 (1.03–1.13) | <.001 |
| Corrected $T_{peak}$ to $T_{end}$ | 89 ± 28 | 72 ± 17 | 1.05 (1.02–1.09) | .002 |
| $QT_{peak}$/QT ratio (%) | 27 ± 6 | 22 ± 4 | 0.83 (0.73–0.94) | .004 |

Models were adjusted for gender and age.
CI = confidence interval; OR = odds ratio; QTc = corrected QT interval; SQTS = short QT syndrome.

provides evidence that increased transmural dispersion of repolarization under short QT interval conditions results in ventricular tachyarrhythmia.[38] A tall peaked T wave is one of the characteristic ECG abnormalities in SQTS,[1] but the amplitude of the T wave is not different between patients with SQTS and subjects with short QT interval and no arrhythmic events, suggesting that a tall T wave is associated with a short QT interval but is not associated with arrhythmogenicity.[26] In SQTS, characteristic ECG abnormities are also found in the early repolarization phase. In patients with SQTS, the ECG shows a very short J-point to T-wave peak interval and no flat ST segment.[26] In our study, early repolarization was frequently found in SQTS and was associated with arrhythmic events. Whether the inferolateral J-point elevation reflects late depolarization or early repolarization is controversial, but this pattern has been considered repolarization because of slower inscription, spontaneous changes occurring concurrently with ST segment but not with QRS complexes, and absence of late potentials on signal-averaged ECG.[9,40] Taken together, the finding suggest that abnormalities in the early phase of repolarization create the arrhythmogenic substrate in SQTS.

Sex hormone and gender difference have an important role in the arrhythmia syndromes.[41–43] It is well known that the QT interval is affected by sex hormones, and the QT interval is longer in women than men.[44] Female gender is a risk factor for development of ventricular tachyarrhythmias in both congenital and acquired long QT syndrome.[41,42] On the other hand, Brugada syndrome is more prevalent in men than in women, and the male hormone testosterone is reported to contribute to male predominance in Brugada syndrome.[43] In this study, male gender was associated with arrhythmic events in SQTS and short QT interval was frequently found in men, suggesting a role of sex hormones in SQTS opposite to that in long QT syndrome. Recent evidence that the QT interval can be shortened by anabolic androgenic steroids and testosterone further supports this hypothesis.[45,46]

SQTS is a genetically heterogeneous disease with five responsible genes encoding ion channels: *KCNQ1*, *KCNH2*, *KCNJ2*, *CACNA2D1*, and *CACNB2b*.[3,4] An increase in outward current by gain-of-function mutations in potassium channels or a decrease in inward current by loss of function mutations in calcium channels may be responsible for SQTS.[3,4] Early repolarization was found in patients with mutations in *KCNQ1* and *KCNH2* and in those without mutations in the known genes, suggesting a heterogeneous genetic background for the association between short QT interval and early repolarization. To date, mutations in calcium channel genes (*CACNA2D1* and *CACNB2b*) have been identified in three probands with Brugada syndrome associated with a short QT interval, but early repolarization is not present in the inferolateral leads in any of them.[4] A recent study has identified a mutation in *KCNJ8*, an initial responsible gene for idiopathic ventricular fibrillation associated with early repolarization.[47] Although there are some similarities in phenotype between SQTS and idiopathic ventricular fibrillation with early repolarization, a common genetic background has not been identified.

## Conclusion

Our study showed a high prevalence of early repolarization in patients with SQTS and an association of early repolarization with arrhythmic events. Early repolarization may be a useful marker for risk stratification of cardiac arrest in SQTS, although further investigation with longitudinal follow-up is required to evaluate our results.

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

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

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

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

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

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

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

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

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

## Methods

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

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

**Abbreviations and Acronyms**

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

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

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

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

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

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

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

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

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

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

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

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

## Results

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

**Table 1 Initial Characteristics of Patients and Control Subjects**

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

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

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