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Original Article

# Flecainide reduces ventricular arrhythmias via a mechanism that differs from that of β-blockers in catecholaminergic polymorphic ventricular tachycardia

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ABSTRACT

*Background:* Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by episodic ventricular tachycardia induced by adrenergic stress. Although β-blockers are used as first-line therapy, their therapeutic effects are largely incomplete. Flecainide has recently been shown to modify the molecular defects in CPVT. The aim of this study was to investigate the effects of flecainide as an add-on to conventional therapy on exercise-induced ventricular arrhythmia and compare them with those of conventional therapy alone.
*Methods:* The study included 5 CPVT patients with a mutation in *RYR2*. They experienced episodic arrhythmic events despite conventional β-blocker therapy and were therefore given flecainide in addition. The effects of the addition of flecainide therapy on ventricular arrhythmia during exercise testing were compared with those of conventional therapy alone.
*Results:* Both β-blockers alone and with additional flecainide increased the maximal workload attained at the onset of ventricular arrhythmia; however, only flecainide increased the sinus rate at the onset of ventricular arrhythmias. Furthermore, flecainide increased the exercise capacity by preventing exercise-induced arrhythmias. During a follow-up period of $17 \pm 2$ months, 1 patient experienced recurrent arrhythmic episodes that were associated with noncompliance. All patients reported improvements in their ability to perform the activities of daily living.
*Conclusion:* Flecainide effectively reduced ventricular arrhythmias via a mechanism that differs from that of β-blockers in genotype-positive patients with CPVT. The specific effects of flecainide may be critical in the improvement noted in the patients' ability to perform daily activities.
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## 1. Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome. Mutations in 3 genes have been identified as causative factors for CPVT: *RYR2*, encoding the cardiac ryanodine receptor (RyR2); *CASQ2*, encoding cardiac calsequestrin; and *KCNJ2*, encoding the inward rectifier potassium channel [1–5]. CPVT is characterized by bi-directional and/or polymorphic ventricular tachycardias induced by adrenergic stress in the absence of structural heart disease and is associated with a high incidence of sudden cardiac death [6–8].

Within the vast therapeutic arsenal of antiarrhythmic agents, β-blockers have been proven to reduce ventricular arrhythmias and improve mortality rates in CPVT patients [1,6–9]. Although implantable cardioverter defibrillators (ICDs) are used to prevent sudden death [10], painful shocks can increase the sympathetic tonus and trigger further arrhythmias, eventually leading to a malignant cycle of ICD shocks and, ultimately, death in patients

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**Table 1**
Patient characteristics and therapy.

| Patient no. | Family no. | Mutation in *RYR2* | Sex | Age at first symptom (yr) | Presenting symptom | Age at diagnosis (yr) | Aborted cardiac arrest | ICD | Conventional therapy, mg (mg/kg body weight) | Presenting symptom before flecainide | Age at treatment with additional flecainide (yrs) | Final drug dosage, mg (mg/kg body weight) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Flecainide | Conventional therapy |
| 1 | 1 | I4587V | F | 15 | Syncope | 37 | No | Yes | Metoprolol 120 (2.36) | Dyspnea | 38 | 100 (1.96) | Metoprolol 60 (1.18) |
| 2 | 1 | I4587V | M | 11 | Syncope | 11 | Yes | No | Metoprolol 40 (1.03) | Syncope | 13 | 100 (2.1) | Metoprolol 40 (1.03) |
| 3 | 2 | R2474G | F | 1 | Syncope | 11 | Yes | Yes | Atenolol 100 (3.2) Verapamil 120 (3.9) | Syncope | 18 | 150 (4.8) | Atenolol 100 (3.2) Verapamil 120 (3.9) |
| 4 | 3 | R407S | M | 12 | Syncope | 13 | No | Yes | Atenolol 100 (2.22) Verapamil 120 (2.67) | Dyspnea | 13 | 100 (2.22) | Atenolol 50 (1.11) |
| 5 | 4 | G2400T | M | 3 | Syncope | 15 | Yes | No | Atenolol 50 (0.97) | Syncope | 15 | 200 (3.86) | Atenolol 50 (0.97) |

ICD, implantable cardioverter defibrillator.

with CPVT [11,12]. From a clinical perspective, therefore, the development of additional therapies to suppress ventricular arrhythmias is highly desirable. Flecainide, a class I sodium channel blocker, has recently been reported to block the RyR2 channel and prevent CPVT episodes [13–15]. However, the difference between β-blockers and flecainide in terms of their respective therapeutic effects in preventing CPVT episodes is yet to be investigated in detail. In the present study, we examined the effectiveness of adding flecainide to β-blocker treatment in inhibiting exercise-induced arrhythmias in CPVT patients with *RYR2* mutations.

## 2. Methods

### 2.1. Patients and study design

Japanese probands and their relatives with a clinical diagnosis of CPVT (based on exercise-induced bidirectional and/or polymorphic VT in the absence of structural cardiac disease) and a putative pathogenic *RYR2* mutation were enrolled in the study. Because the effects of conventional therapy with the maximum tolerable dose of β-blockers with or without verapamil were insufficient, all patients in this study were treated with flecainide. The dose of flecainide was adjusted according to the highest tolerable dose at the discretion of the treating physicians. Patients treated with flecainide were followed up at our outpatient clinic every 1–2 months. This study was approved by the institutional review boards at each of the participating institutions.

### 2.2. Effects of flecainide

Exercise testing using the standard Bruce protocol was performed under 3 conditions: in the absence of any medication, with β-blocker therapy, and with β-blocker therapy and flecainide. Patients underwent exercise testing after receiving treatment for more than 2 weeks. The dosage of each drug for each patient is shown in Table 1. Exercise testing was repeated as per the same protocol until at least the workload equivalent to that achieved during the previous test was attained, so long as no severe symptoms requiring termination of exercise were noted. The end-point of the exercise test was attainment of the target heart rate, occurrence of frequent premature ventricular ectopy (PVE), non-sustained VT, leg fatigue, or dyspnea. The numbers of PVEs (i.e., isolated PVE, bigeminal rhythm of PVE, bidirectional VT, polymorphic VT, and VT [sustained or non-sustained]) were counted. Sinus heart rate at the onset of ventricular arrhythmias was calculated from the last sinus RR interval. Ventricular arrhythmias were scored as described previously [15]: 1, no or isolated PVE; 2, bigeminal PVE and/or frequent PVE ( $>10$ per min); 3, couplet; and 4, non-sustained VT ( $>3$ successive PVEs). A ventricular arrhythmia score of 1 was considered as complete suppression of ventricular arrhythmias, whereas other improvements in the ventricular arrhythmia score were considered partial suppression. Patients were followed up for arrhythmia recurrences at our outpatient clinic every 1–2 months.

### 2.3. Statistical analysis

Continuous data are presented as mean $\pm$ standard deviation or median (range), and categorical variables are presented 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. A two-tailed $P$ value of $<0.05$ was considered statistically significant. Statistical analysis was performed using JMP version 7.0.1 (SAS Campus Drive, Building T, Cary, NC, USA).

## 3. Results

### 3.1. Patient characteristics

Five genotype-positive CPVT patients from 4 families were administered flecainide therapy in addition to conventional therapy (Table 1). Patient 2 was the son of patient 1. Data on patient 3 have also been reported elsewhere [15]. Two patients were female. The mean age at the first CPVT episode was $8 \pm 6$ years (range, 1–15 years). Prior to treatment with flecainide, all patients had experienced ventricular arrhythmias and/or symptoms induced by physical or emotional stress, despite the use of maximum tolerable doses of β-blockers with or without verapamil.

Flecainide was started at the age of $19 \pm 11$ years (range, 13–38 years). After the addition of flecainide, the dosage of conventional therapy was modified in patients 1 (reduction of β-blocker dosage) and 4 (reduction of β-blocker dosage and discontinuation of verapamil) because of sinus bradycardia. It should be noted that flecainide caused no side effects in any of the patients enrolled in this study. Flecainide prolonged the PR interval (from $138 \pm 23$ ms without flecainide to $163 \pm 13$ ms with flecainide; $P<0.05$), but did

not affect the QRS duration (82 ± 6 ms without flecainide and 80 ± 7 ms with flecainide; $P=0.68$) or the corrected QT interval (389 ± 27 ms without flecainide and 394 ± 40 ms with flecainide; $P=0.79$). The values for these parameters remained within the normal range at rest and during exercise testing in all patients.

### 3.2. Effects of flecainide during exercise testing

Exercise testing was performed at baseline without the use of any medication, on conventional therapy with β-blockers, and after the addition of flecainide to conventional therapy. Patients 4 and 5 did not undergo baseline exercise testing because severe arrhythmic events were easily induced in these patients. Exercise testing was repeated as per the same protocol until at least the workload attained in the previous test was achieved in all patients. We initially studied the effects of β-blockers on exercise-induced ventricular arrhythmias in 3 patients who had undergone baseline testing (patients 1–3) (Fig. 1). β-Blockers decreased the frequency of PVE in 1 patient, but did not suppress VT in the remaining 2 (Fig. 1). β-blockers reduced the heart rate in response to exercise compared to the baseline values obtained without the administration of any medication and also suppressed the incidence of PVE during exercise in cases that showed PVE during baseline testing. However, the use of β-blockers did not result in any notable changes in the maximum number of PVEs observed compared to that observed during baseline testing. Furthermore, the sinus rate at the onset of PVE was identical at baseline testing and with the use of β-blockers.

We then studied the effects of adding flecainide to conventional therapy on exercise-induced ventricular arrhythmias in 5 patients (Fig. 2). Flecainide suppressed VT in 3 patients (patients 1–3), including 1 (patient 3) in whom flecainide completely suppressed ventricular arrhythmias (Fig. 2). In the remaining 2 patients (patients 4 and 5), although flecainide did not result in any changes in the ventricular arrhythmia scores (Fig. 3), the drug effectively increased the exercise workload at the onset of ventricular arrhythmias. Furthermore, flecainide improved the maximum workload attained in 3 patients (Table 2). During exercise testing after treatment with flecainide, ventricular arrhythmias developed at a later stage and the sinus rate at the onset of ventricular arrhythmias increased in comparison to the observations made during exercise testing after treatment with conventional therapy alone in all patients except for 1, who did not have ventricular arrhythmias while on treatment with flecainide (Table 2). Interestingly, the response in terms of heart rate to exercise stress was similar for treatment with conventional therapy alone and that with additional flecainide, despite the favorable effects of flecainide observed in 2 patients (Fig. 3, patients 2 and 4).

### 3.3. Clinical follow-up

During a followup of 17 ± 2 months (range, 15–20 months), 4 patients who received a combination of flecainide with conventional therapy did not develop recurrences of arrhythmias. Patient 2 did not develop arrhythmias for 17 months after the addition of flecainide; however, arrhythmic events later developed because of noncompliance with the prescribed treatment regimens. This patient was immediately administered therapy and did not experience any further events. Notably, all patients reported improvements in their ability to perform activities of daily living after the addition of flecainide at their follow-up

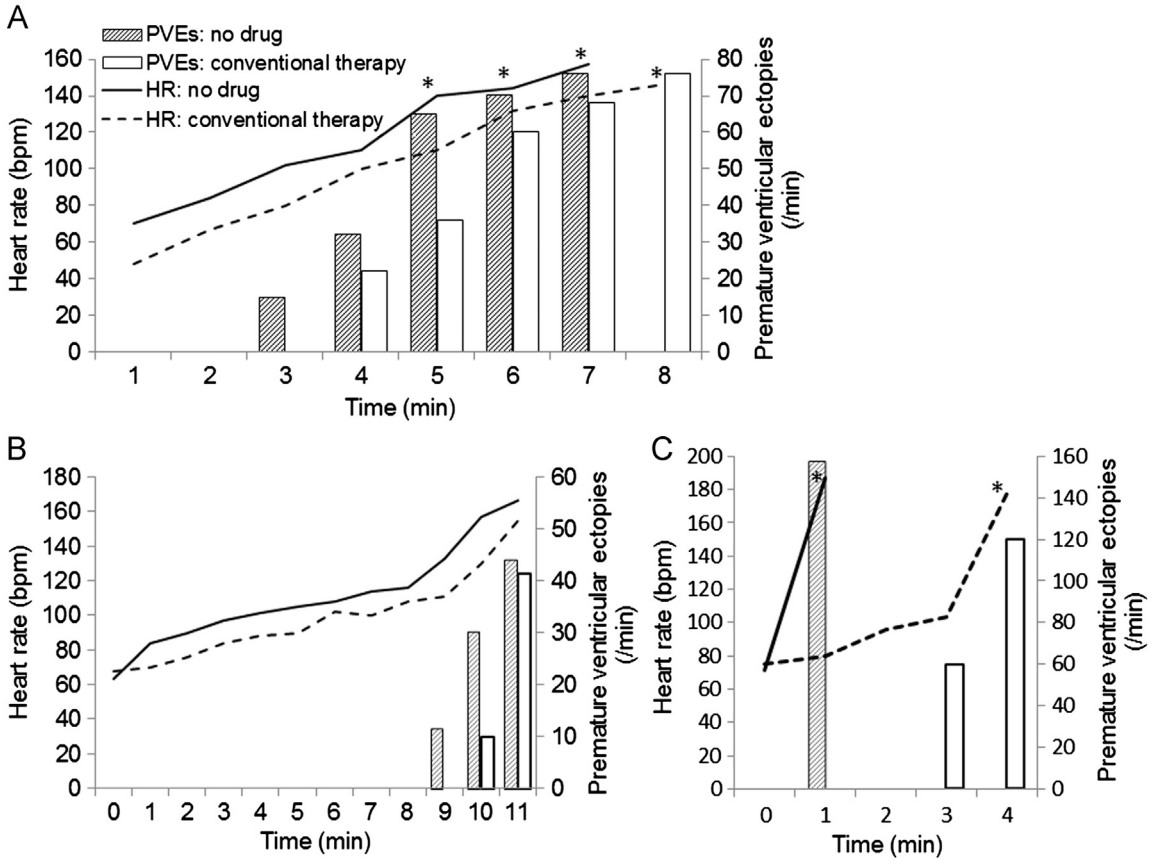


**Fig. 1.** Ventricular arrhythmias during exercise testing without any drug therapy and with conventional therapy. Sinus heart rate (HR) and the number of instances of premature ventricular ectopies (PVEs) in every minute are shown for 3 patients who underwent exercise testing without any drug therapy (A, patient 1; B, patient 2; C, patient 3). The final point for HR indicates the end of exercise. Asterisks indicate the occurrence of ventricular tachycardia.

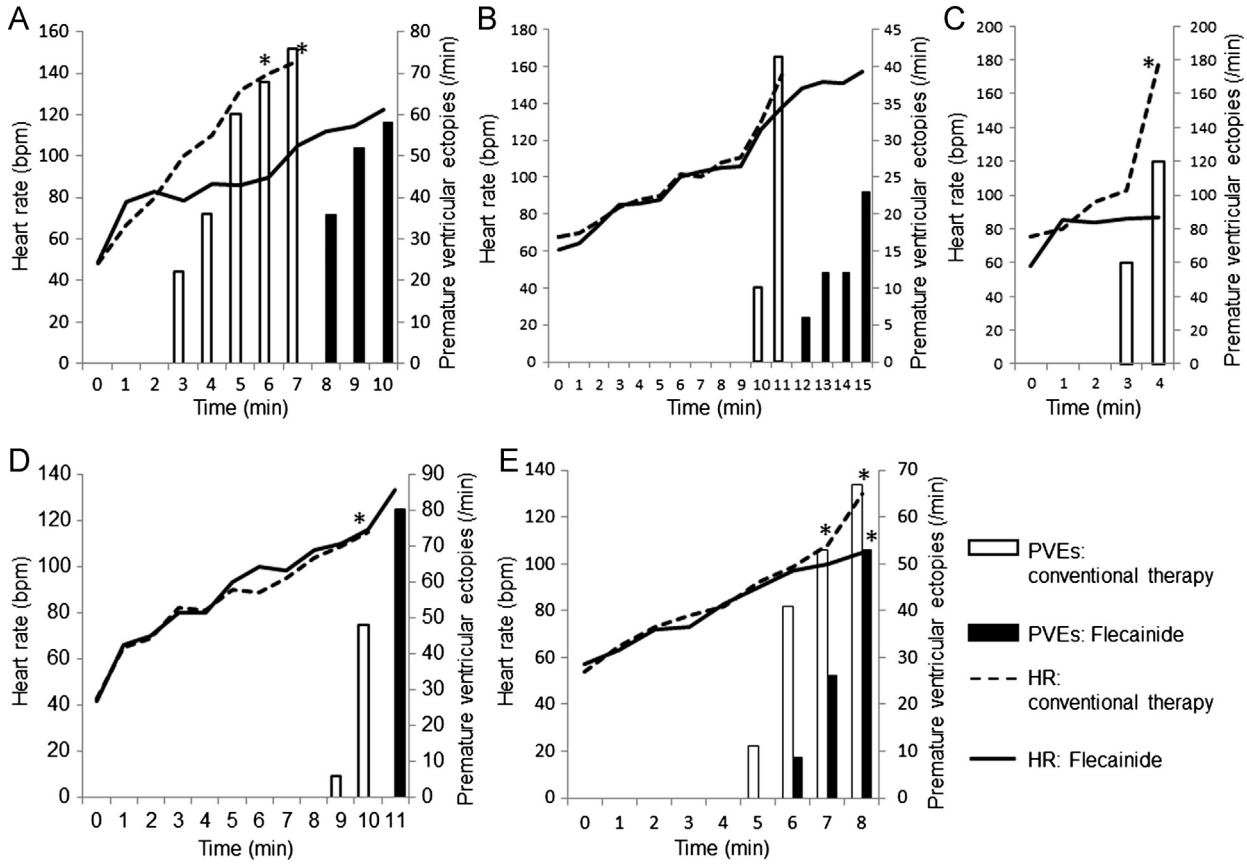


**Fig. 2.** Effects of flecainide in addition to conventional therapy on exercise-induced ventricular arrhythmias. Sinus heart rate (HR) and the number of instances of premature ventricular ectopies (PVEs) were compared between treatment with conventional therapy alone and treatment with flecainide in addition to conventional therapy. Asterisks indicate the occurrence of ventricular tachycardia (A, patient 1; B, patient 2; C, patient 3; D, patient 4; E, patient 5).

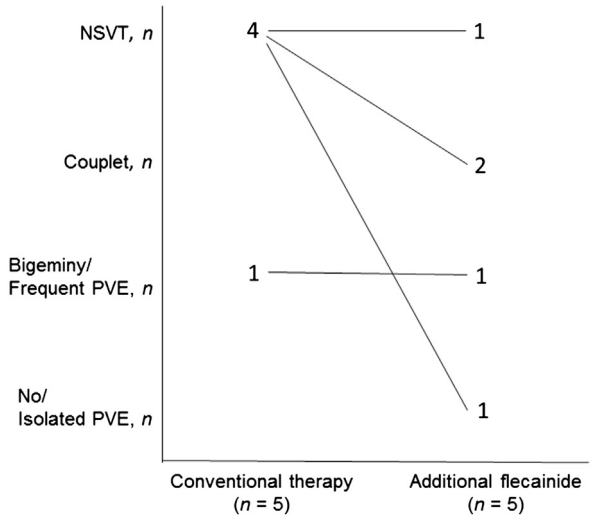


**Fig. 3.** Ventricular arrhythmia score during exercise testing with conventional therapy alone and with flecainide in addition to conventional therapy. PVE, premature ventricular ectopy; NSVT, non-sustained ventricular tachycardia.

visits. All patients showed good tolerance to flecainide, and none developed severe side effects.

## 4. Discussion

The present study showed that flecainide suppresses CPVT in a manner that differs from that of β-blockers. Although flecainide increased the sinus rate at the onset of ventricular arrhythmias, β-blockers failed to demonstrate such a change, despite the fact that both flecainide and β-blockers increased the exercise workloads at the onset of ventricular arrhythmias. Furthermore, flecainide facilitated increased exercise capacity by preventing PVE and improved the performance of activities of daily living. Consequently, this considerably ameliorated the patient's quality of life.

Because ventricular tachyarrhythmias are induced by adrenergic stress in patients with CPVT, anti-adrenergic therapy—primarily achieved by the use of β-blockers—has been widely used to suppress CPVT [6–9,16]. Unfortunately, the effect of β-blockers on suppressing recurrences of ventricular tachyarrhythmias is ultimately incomplete [7,8]. In the present study, β-blockers reduced the response in terms of heart rate to exercise and increased the exercise workload at the onset of ventricular arrhythmias, which could be attributed to the anti-adrenergic properties of the drug, but failed to increase heart rate at the onset of arrhythmias. In contrast, flecainide increased the heart rate at the onset of arrhythmias during exercise testing and suppressed ventricular arrhythmias even at higher heart rates, suggesting that this unique action may be crucial in the suppression of CPVT.

Spontaneous $Ca^{2+}$ release from the destabilized RyR2 complex in the sarcoplasmic reticulum triggered by adrenergic stress is the mechanism underlying CPVT [17–19], and thus, the suppression of spontaneous $Ca^{2+}$ release could potentially be of therapeutic value for CPVT. Flecainide was recently shown to directly reduce the probability of RyR2 channels being open in the sarcoplasmic reticulum, thereby suppressing triggered beats [13,14]. The drug also decreases the activity of $Na^{+}/Ca^{2+}$-exchangers via inhibition of the $Na^{+}$ channel, which in turn reduces intracellular $Ca^{2+}$ overload and thereby the rate of triggered beats [13,14]. Furthermore,

**Table 2**
Effects of the addition of flecainide to conventional ther7apy during exercise testing.

| | No drug | | | | Conventional therapy | | | | | | | Additional flecainide | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patient no. | | | Mean ± SD | Patient no. | | | | | Mean ± SD | *P* value ($n=3$)[a] | Patient no. | | | | | mean ± SD | *P* value ($n=5$)[b] |
| | 1 | 2 | 3 | | 1 | 2 | 3 | 4 | 5 | | | 1 | 2 | 3 | 4 | 5 | | |
| Sinus rate at rest (bpm) | 70 | 74 | 71 | 71.7 ± 1.7 | 50 | 53 | 71 | 44 | 54 | 54.4 ± 9.0 | 0.183 | 52 | 62 | 58 | 42 | 57 | 54.2 ± 6.9 | 0.96 |
| Sinus rate at maximal exercise (bpm) | 157 | 166 | 187 | 170.0 ± 12.6 | 140 | 155 | 178 | 127 | 130 | 146.0 ± 18.8 | < 0.05 | 123 | 141 | 87 | 133 | 112 | 119.2 ± 18.8 | 0.18 |
| Maximum workload attained, METs | 7.4 | 13.5 | 3 | 8.0 ± 4.3 | 8.6 | 13.5 | 5.8 | 11.6 | 10.2 | 9.9 ± 2.6 | 0.242 | 11.6 | 14.3 | 5.8 | 13.5 | 10.2 | 11.1 ± 3.0 | 0.12 |
| Time at the onset of ventricular arrythmias (s) | 140 | 559 | 35 | 244.7 ± 226.4 | 210 | 581 | 180 | 582 | 288 | 368.2 ± 177.7 | 0.158 | 437 | 740 | – | 620 | 318 | 528.8 ± 162.6 | 0.10[c] |
| Sinus rate at the onset of ventricular arrhythmias (bpm) | 102 | 133 | 103 | 112.7 ± 14.38 | 100 | 130 | 103 | 109 | 92 | 106.8 ± 12.8 | 0.199 | 112 | 138 | – | 130 | 97 | 119.3 ± 15.9 | < 0.05[c] |
| Maximum no. of PVEs in 1 min | 76 | 44 | 157 | 92.3 ± 47.6 | 76 | 41 | 120 | 48 | 67 | 70.4 ± 27.8 | 0.378 | 52 | 30 | 0 | 80 | 53 | 43 ± 26.7 | 0.75[c] |
| Ratio of PVEs to sinus beats during a 10-sec period | 0.48 | 0.27 | 0.84 | 0.53 ± 0.24 | 0.54 | 0.26 | 0.67 | 0.38 | 0.52 | 0.47 ± 0.14 | 0.648 | 0.42 | 0.21 | 0.00 | 0.60 | 0.47 | 0.34 ± 0.21 | 1.00[c] |

METs, metabolic equivalents; PVE, premature ventricular ectopy.
[a] No drug versus conventional therapy.
[b] Conventional therapy versus additional flecainide.
[c] $N=4$.

flecainide increases the inward rectifier $K^+$ current generated by Kir2.1 channels by reducing their affinity for intracellular polyamines and stabilizes the resting membrane potential, resulting in the suppression of triggered activity [20]. These multiple effects of flecainide may explain the mechanism by which the drug effectively prevents ventricular arrhythmias even at higher sinus rates during exercise and thus increases the heart rate at the onset of ventricular arrhythmias.

## 5. Study limitations

Although the number of CPVT patients enrolled in the present study was small, we documented clearly discernible effects of flecainide on CPVT during exercise testing. The dose of flecainide was adjusted to increase it to the maximum tolerable dose without monitoring serum concentrations. We studied the effects of flecainide in combination with conventional therapy in patients whose arrhythmias were uncontrolled on treatment with conventional therapy. The effect of flecainide was evaluated by exercise testing, as was done in previous studies, and the reproducibility of the effects of flecainide during exercise testing has been reported [7,15]. However, variability in exercise test results cannot be completely ignored and exercise testing may not accurately predict the occurrence of fatal arrhythmic events [7]. Exercise testing prior to the initiation of conventional therapy was not performed for 2 patients whose severe arrhythmic events were easily induced. The aim of this study was to compare the efficacy of conventional therapy and the addition of flecainide on exercise-induced ventricular arrhythmias.

## 6. Conclusion

Flecainide showed multiple pharmacological effects—some of which differ from those of β-blockers—in patients with CPVT. The unique effects of flecainide may explain the favorable changes noted in patients whose arrhythmias were refractory to conventional therapy. Flecainide was also effective in increasing exercise capacity at the onset of ventricular arrhythmias, which is assumed to be a crucial factor in the improvement documented in the patients' overall quality of life.

## Conflict of interest

The authors indicated no potential conflict of interest.

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