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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

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

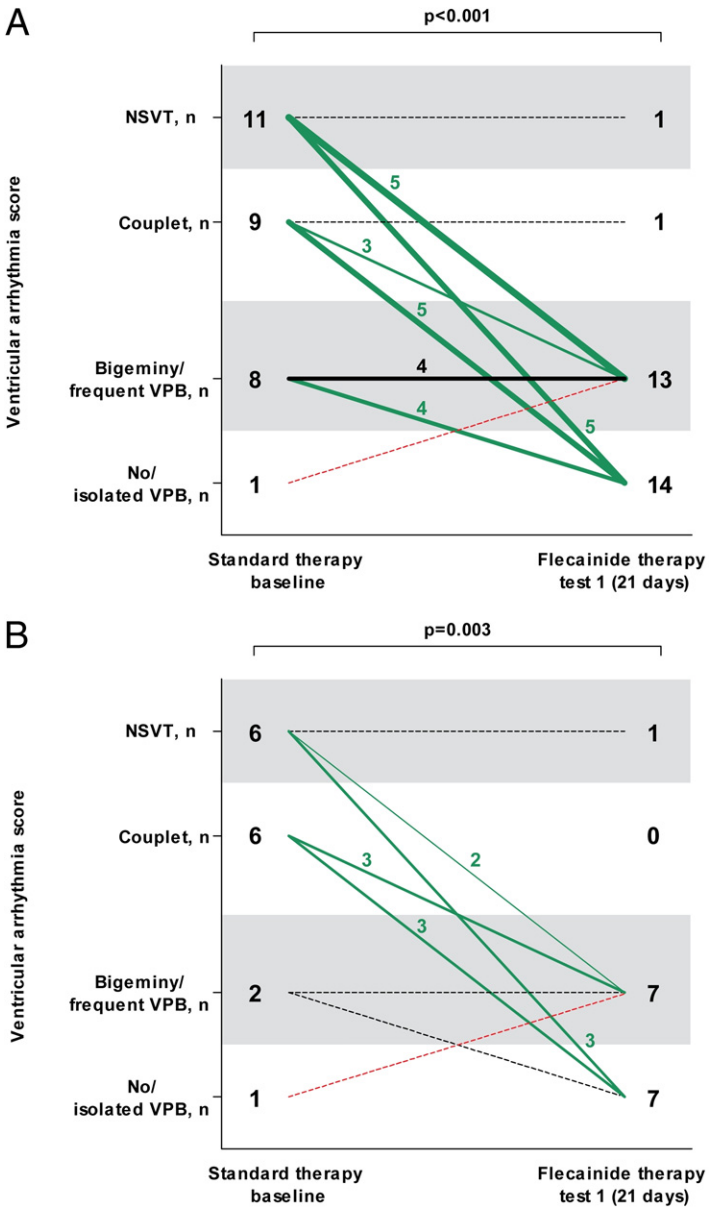

Figure 1 **Ventricular Arrhythmia Score on Standard Therapy and on Flecainide**

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-

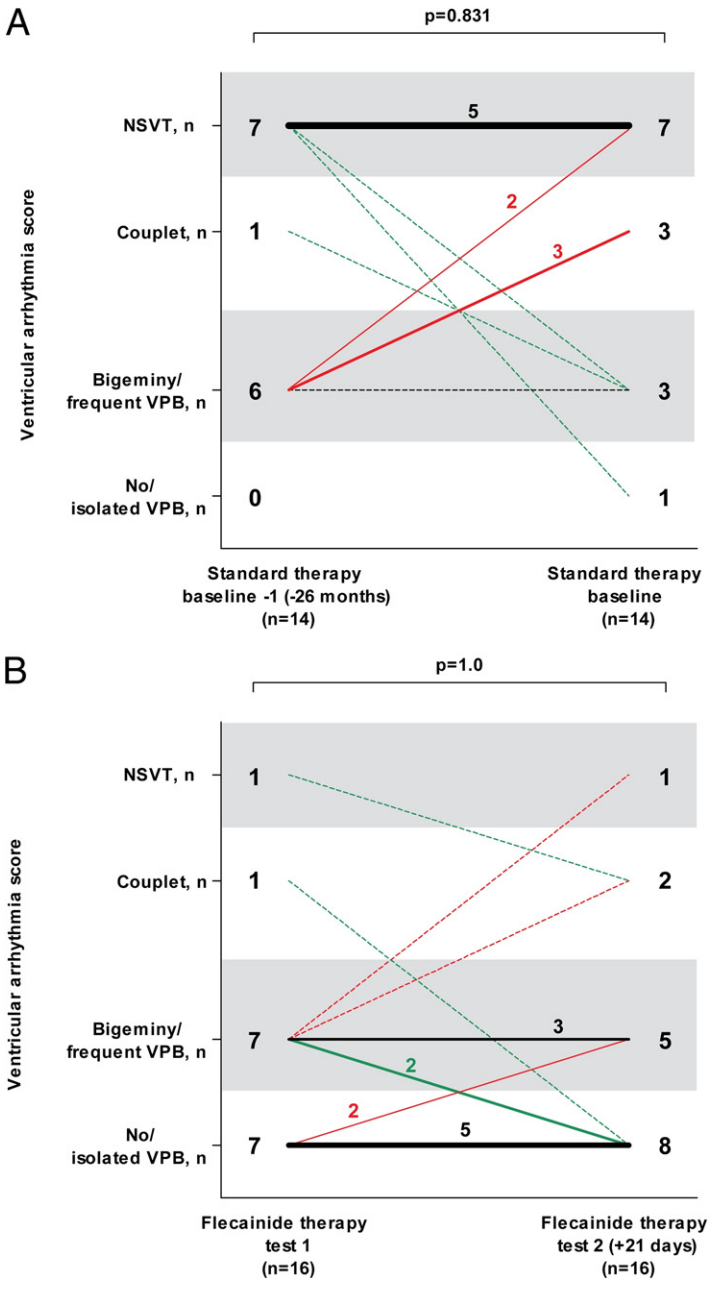

Figure 2 **Reproducibility of Ventricular Arrhythmia Score on Exercise Testing**

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

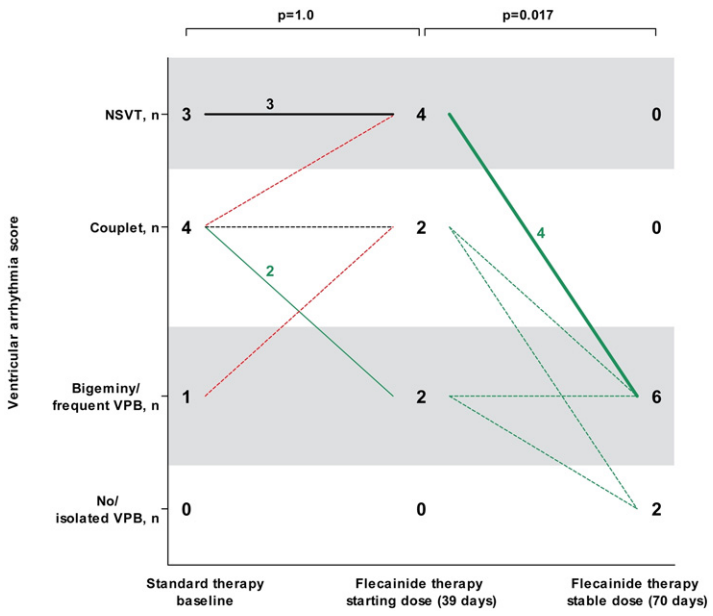

Figure 3 **Dose Dependence of Flecainide in 8 CPVT Patients Who Had an Increase in Flecainide Dose**

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.