Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia

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Abstract

Objective—This study evaluated the efficacy and safety of flecainide in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) on top of conventional drug therapy.

Background—CPVT is an inherited arrhythmia syndrome caused by gene mutations that destabilize cardiac ryanodine receptor Ca^{2+} release channels. Sudden death is incompletely prevented by conventional drug therapy with β-blockers +/− Ca^{2+} channel blockers. The anti-arrhythmic agent flecainide directly targets the molecular defect in CPVT by inhibiting premature Ca^{2+} release and triggered beats *in vitro.*

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Methods—We collected data from every consecutive genotype-positive CPVT patient started on flecainide at eight international centers before November 13, 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 of 25 years, range 7 to 68; 70% female). Exercise tests comparing flecainide with conventional therapy alone were available in 29 patients. Twenty-two (76%) patients had either a partial (n=8) or complete (n=14) suppression of exercise-induced ventricular arrhythmias by flecainide (p<0.001). No patient experienced worsening of exercise-induced ventricular arrhythmias. 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) one patient experienced ICD shocks for polymorphic ventricular arrhythmias, which was associated with low flecainide levels. In one patient, flecainide successfully suppressed exerciseinduced ventricular arrhythmias for 29 years.

Conclusions—Flecainide reduced exercise-induced ventricular arrhythmias patients with CPVT uncontrolled by conventional drug therapy.

Keywords

antiarrhythmia agents; catecholaminergic polymorphic ventricular tachycardia; ventricular arrhythmia

Introduction

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 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 (*CASQ2*) (4–6), and these cause spontaneous *RyR2* channel openings (7,8). The ensuing rise in cytosolic Ca^{2+} triggers delayed afterdepolarizations, ventricular premature beats (VPBs), and VT, 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 with ventricular arrhythmias on β-blocker. 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 receiving 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 two highly symptomatic CPVT patients (23).

Here we collate the data from every CPVT patient started on flecainide at eight 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 every consecutive CPVT patient in whom flecainide was started at eight tertiary referral centers in the Netherlands, Canada, France, Israel, Japan, and the United States before November 13, 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 *CASQ2*. Decisions on flecainide starting dose and dosing increases were made by the treating physician as part of specialized clinical care. Data collection and analysis was done retrospectively by chart review and was approved by the review boards at each participating institution.

Primary and secondary outcome measures

Couplets or VT during exercise are significantly associated with future arrhythmic events in CPVT (2). Since 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 below) of the last exercise test on conventional therapy with the ventricular arrhythmia score of the first exercise test after a minimum of five 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 treadmill (standard or modified Bruce protocols), or bicycle ergometer.

Secondary outcome measures were the incidence of arrhythmic events (defined as syncope, aborted sudden cardiac death, 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 predefined 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 minute), 3=couplet, 4=non-sustained VT (NSVT; 3 successive VPBs));

2. Presence of either of the parameters of the ventricular arrhythmia score, and 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 ectopy, most often an isolated VPB;

4. Maximum number of VPBs during a 10-seconds period;

5. Ratio of VPBs/sinus beats during the 10-seconds period with the maximum number of VPBs. Reaching a ventricular arrhythmia score of one was considered *complete* suppression of ventricular arrhythmias. Other ventricular arrhythmia score improvements were considered *partial* suppression.

Statistical analysis

Continuous data are presented as mean ± standard deviation or median (range), and categorical variables as number (percentage). Related samples were compared using the paired Wilcoxon signed ranks 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 two-tailed p value <0.05 was considered statistically significant. Statistical analysis was carried out with SPSS software package, version 15.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 33 genotype-positive CPVT patients from 21 families were started on flecainide at eight tertiary care centers (Table 1). All patients had persistent physical or emotional stress-induced ventricular arrhythmias documented by exercise testing, Holter recordings, or the ICD interrogation, and/or persistent symptoms of palpitations, syncope, cardiac arrest, or appropriate ICD shocks, while on β-blockers +/– Ca^{2+} channel blockers. Twenty-three (70%) of the patients were female. The median age at the start of flecainide therapy was 25 (range 7 to 68) years. Thirty-one (94%) patients were treated with β-blockers, and four (12%) of them also received Ca^{2+} channel blockers (Table 1). In one patient (#13), flecainide was stopped because of side effects before exercise testing could be repeated, in another patient (#27) the β-blocker dose was increased during flecainide treatment, and two 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 (59%) patients, baseline exercise testing was performed less than 48 hours before flecainide initiation.

Flecainide therapy reduces exercise-induced ventricular arrhythmias

Flecainide treatment improved the ventricular arrhythmia score in 22 (76%) patients (p<0.001; Figure 1A). Fourteen (48%) patients had complete suppression of ventricular arrhythmias (including seven patients without any VPB), and 8 (28%) had partial suppression. None of the patients experienced significant (ie, couplet or VT) worsening of the exercise-induced ventricular arrhythmia score (Figure 1A).

Flecainide treatment also significantly improved all other predefined parameters of exercise-induced ventricular arrhythmia (Table 2). For example, patients on flecainide achieved significantly higher heart rates before ventricular ectopy 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 vs. 160±24 ms; p=0.003), and the QRS duration (83±9 vs. 89±11 ms; p=0.005), but did not change the QTc interval (399±26 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 one patient (#20).

We next assessed the reproducibility of exercise testing as a measure of the ventricular arrhythmia burden in CPVT. While not available for all patients, a subset of patients underwent repeated exercise testing either on the same dose of conventional therapy (n=14), or on the same flecainide dose (n=16). In both cases, the ventricular arrhythmia score of the second exercise test was not statistically different from that of the first exercise test (Figure 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-seconds

period was 5±5 at the first exercise test on the stable flecainide dose, and 6±6 at the second exercise test on 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 per 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; Figure 1B), and all other predefined arrhythmia parameters in this subgroup to a similar extent as in the primary analysis.

The ventricular arrhythmia score in the two 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 to patients with either partial (142±38 mg, n=6) or complete ventricular arrhythmia suppression (150±60 mg, n=12). Eight (24%) patients 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 exercise-induced ventricular arrhythmia score (Figure 3).

Clinical follow-up

Three patients (#13, #30 and #31) discontinued flecainide with less than six months of follow-up due to side effects. One 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 two 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 reduced in five patients (#4, #5, #6, #9, and #12) who had a partial suppression of ventricular arrhythmias on flecainide and suffered from side effects of β-blocker therapy (in particular fatigue) before flecainide was started. One patient (#29) refused to take beta-blockers during follow-up, with no worsening of exercise-induced ventricular arrhythmias on flecainide monotherapy.

Thus, 30 out of 33 (91%) patients continued to receive flecainide and were included in the further analysis on the incidence of arrhythmic events. During a median follow-up of 20 months (range 12 to 40 (excluding patient 32#)), VT recurred in only one patient (#1) who experienced several appropriate ICD shocks for polymorphic VT after eight months of flecainide treatment. Her serum flecainide levels were low (0.34 mcg/mL) at the time of the event compared to levels obtained previously (0.75 to 0.82 mcg/mL), suggesting non compliance. She was hospitalized for 48 hours, 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 have 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 daily) was added to sotalol (160 mg daily), which resulted in complete suppression of ventricular arrhythmia during exercise testing. Subsequent genotyping revealed a mutation in *RYR2.* In 2008, an exercise test 48 hours after stopping flecainide and sotalol showed NSVT. After restarting the combined therapy, a subsequent exercise test only showed isolated VPBs, but no VT. In patient #33 flecainide 150 mg daily was started in 2007 because of two syncopes with ventricular fibrillation on the ICD interrogation despite nadolol 240 mg daily. Exercise testing showed complete suppression of ventricular arrhythmias and she has been free from 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 on 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 on top of β-blocker therapy should be considered for CPVT patients that otherwise have few alternative therapeutic options. The optimal dose appears to be between 150 to 200 mg daily, with a range from 100 to 300 mg. Daily doses less than 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 CASQ2 (4,5), two proteins that control Ca^{2+} release from the sarcoplasmic reticulum (SR). 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 rise of intracellular Ca^{2+} in turn activates the electrogenic Na^+/Ca^{2+} exchanger (NCX), 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) Flecainide'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 SR 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 SR 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 is potentially life-saving. β-blockers are considered first-line therapy. In the largest published series of patients with CPVT, the risk for cardiac arrest (defined as sudden cardiac death, aborted cardiac arrest, and appropriate ICD shocks) 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 are survivors of cardiac arrest, or when syncope or sustained VT persists despite maximal tolerable β-blockade (33). Yet, ICDs have 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 six patients treated with verapamil and β-blockers after failure of β-blockers alone, reported by Rosso in 2007 (27), three had clinically significant ventricular arrhythmias during 37±6 months of follow-up (36). Other pharmacologic 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 eight 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 ventricular 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 ten months in the Cardiac Arrhythmia Suppression Trial (CAST). 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 from 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, as they received an unusual β-blocker for CPVT or a low β-blocker dose for reasons that were 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 (Figure 1B).

Conclusion

In conclusion, 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.

Acknowledgments

Abbreviations

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CASQ2	cardiac calsequestrin
RYR2	cardiac ryanodine receptor
CPVT	catecholaminergic polymorphic ventricular tachycardia
ICD	implantable cardioverter-defibrillator
NSVT	non-sustained VT
VPB	ventricular premature beats
VT	ventricular tachycardia

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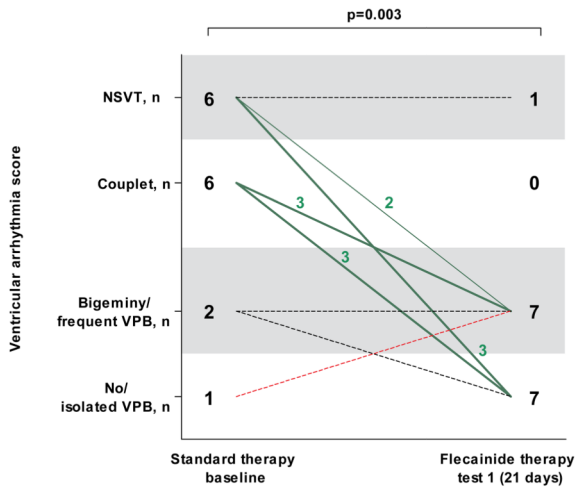
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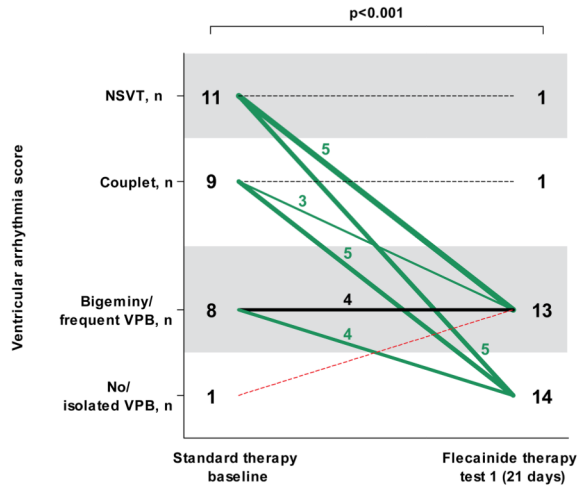
B

Figure 1. Ventricular arrhythmia score per patient at the baseline exercise test on standard therapy and at the first exercise test on the final (stable) flecainide dose in the entire cohort (n=29; panel A), and in the patients who were treated with a first-line β-blocker at an optimal dose (N=15, panel B)

NSVT indicates nonsustained ventricular tachycardia; VPB, ventricular premature beat. The number of patients in each ventricular arrhythmia category and change of ventricular arrhythmia category is shown. The line thickness indicates the number of patients, a dotted line represents one patient. The median time interval between the two tests is shown. All exercise tests were on an unchanged β-blocker dose.

A

B

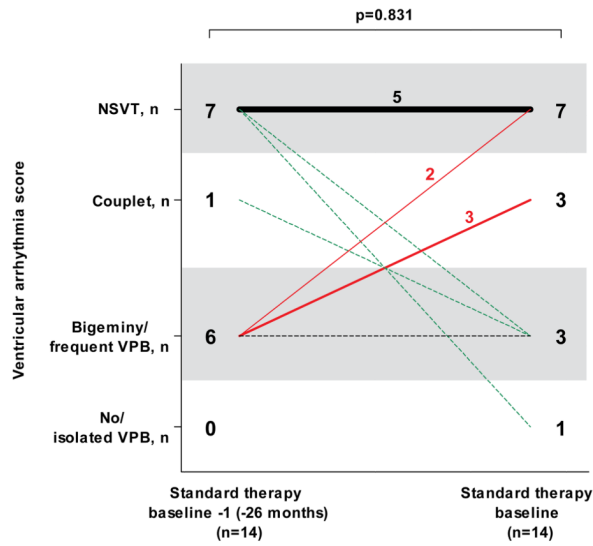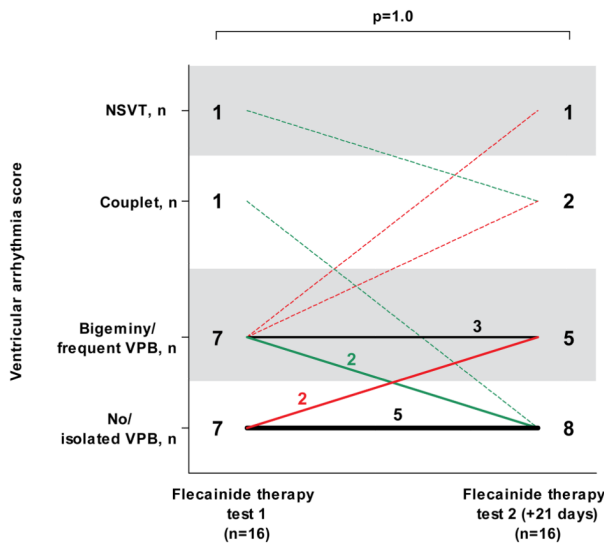**Figure 2. Ventricular arrhythmia score per patient at the baseline exercise test and at the previous exercise test on the same standard therapy dose (panel A), and at the first and second exercise test on the final (stable) flecainide dose (panel B)**

The number of patients in each ventricular arrhythmia category and change of ventricular arrhythmia category is shown. The line thickness indicates the number of patients, a dotted line represents one patient. The median time interval between the two tests is shown. The standard therapy exercise tests were on the same β-blocker +/– Ca^{2+} channel blocker doses. All exercise tests on flecainide were on the same, stable flecainide dose in combination with an unchanged or lower β-blocker dose. The sinus rate at maximal exercise at the first and second exercise test on flecainide was not significantly different (140±19 vs. 144±20; p=0.245). However, the two patients with a ventricular arrhythmia score of 4 and 3 at the

second exercise test did reach a significantly higher maximum sinus rate as compared with the first exercise test (increase of 32 and 19 beats per minute, respectively).
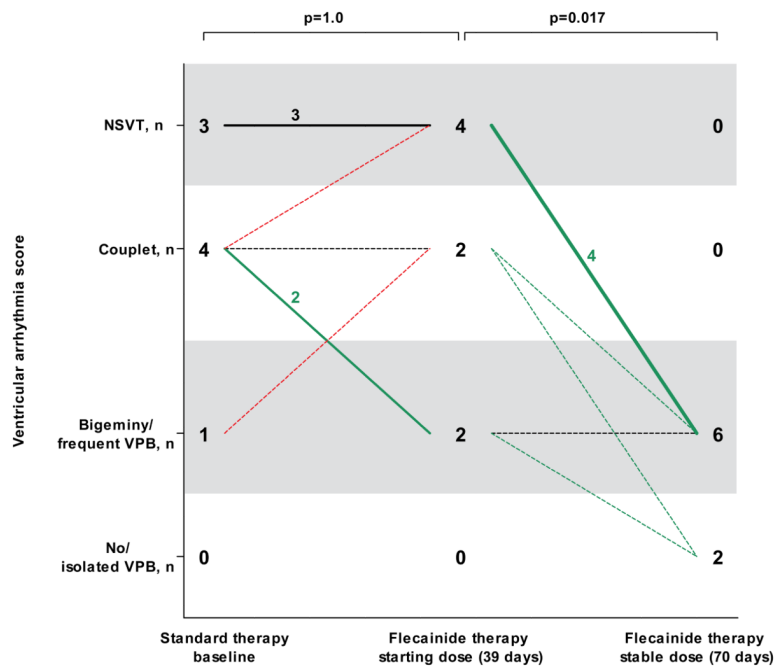
Figure 3. Dose-dependence of flecainide in eight CPVT patients who had an increase inflecainide dose

VPB indicates ventricular premature beat; NSVT, nonsustained ventricular tachycardia. The number of patients in each ventricular arrhythmia category and change of ventricular arrhythmia category (X-axis) at the last exercise test on the starting flecainide dose (96±28 mg; range 50 to 150 mg) and at the first exercise test on the final (stable) flecainide dose (178±78 mg; range 100 to 300 mg) is shown. The line thickness indicates the number of patients, a dotted line represents one patient. The median time interval from the start of flecainide therapy is displayed. All exercise tests were on an unchanged β-blocker dose.

Table 1

Baseline characteristics and flecainide therapy parameters

Patient	Sex	Mutation*	Age at first symptom, years	Proband or relative	Presenting symptom	Age at diagnosis, years	Cardiac arrest	ICD	Age at baseline, years	Drug therapy at baseline, mg (mg per kg body weight)	Indication for starting flecainide treatment	Daily starting / stable flecainide dose, mg (mg per kg body weight)†	Follow-up, months	Response to flecainide treatment	Side effects of flecainide
1‡	Female	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	No
2	Female	R2401H	6	Proband	Syncope	6	No	No	7	Nadolol 15 (0.9)	NSVT (on Holter recordings)	96 (5.6)/120 (7.1)	22	No	No
3‡	Male	CASQ2: 532-1G>A (38)	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	No
4‡	Female	E4076K	28	Relative	Syncope	31	No	No	37	Metoprolol 100 (1.6)	Couplets + side effects	100 (1.6)/150 (2.4)	23	Partial	No
5	Female	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	No
6	Female	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	Female	S4124G	26	Relative	Cardiac arrest	26	Yes	No	41	None||	NSVT	150 (2.2)	22	Partial	Dizziness
8‡	Male	S4124G	8	Relative	Syncope	8	No	No	10	Metoprolol 50 (1.9)	Couplets	50 (1.9)/100 (3.7)	22	Partial	No
9‡	Male	E4187Q	NA	Proband	None (detected by cardiological examination after SCD son)	47	No	No	53	Metoprolol 200 (2.4)	NSVT + side effects	150 (1.7)	20	Partial	No
10‡	Male	E4187Q	NA	Relative	None	19	No	Yes	25	Metoprolol 200 (2.7)	NSVT	150 (2.0)	20	No	No
11‡	Female	E4187Q	NA	Relative	None	14	No	Yes	20	Metoprolol 150 (2.6)	NSVT	100 (1.8)	20	Complete	No
12‡	Male	E4187Q	NA	Relative	None	11	No	Yes	17	Metoprolol 100 (1.6)	NSVT	100 (1.6)/300 (4.8)	20	Partial	No
13	Female	E1724K	13	Relative	Syncope	13	No	No	25	Metoprolol 25 (0.4)	Couplets	100 (1.3)#	NA#	NA#	Fatigue, dizziness, chest pain
14	Female	E1724K	9	Proband	Syncope	15	No	No	50	Sotalol 160 (2.1)	Bigeminy/frequent VPBs + side effects	100 (1.3)	20	No	No
15‡	Male	R420W	NA	Relative	None	38	No	No	49	Metoprolol 100 (1.3)	Couplets	150 (1.9)/300 (3.9)	19	Complete	No
16‡	Male	R420W	NA	Relative	None	12	No	No	16	Metoprolol 100 (1.7)	NSVT	100 (1.7)	19	Complete	No
17	Female	Y4962C	NA	Relative	None	41	No	No	45	Atenolol 25 (0.4)	NSVT	150 (2.5)	12	Complete	No
18‡	Female	M2605V, A4510T, l4757-6_7Cl>TA	NA	Proband	None (detected by exercise testing at preparticipation screening)	40	No	No	40	Metoprolol 100 (1.4)	Couplets	200 (2.9)	18	Partial	No

Patient	Sex	Mutation*	Age at first symptom, years	Proband or relative	Presenting symptom	Age at diagnosis, years	Cardiac arrest	ICD	Age at baseline, years	Drug therapy at baseline, mg (mg per kg body weight)	Indication for starting flecainide treatment	Daily starting/stable flecainide dose, mg (mg per kg body weight)†	Follow-up, months	Response to flecainide treatment	Side effects of flecainide
19	Female	R420W	33	Proband	Syncope	33	No	Yes	36	Bisoprolol 5 (0.08)	Bigeminy/ frequent VPBs	100 (1.5)	17	Complete	No
20	Male	R420W	NA	Relative	None	11	No	No	12	Atenolol 25 (0.7)	Couplets	100 (2.6)	23	Complete	No
21‡	Female	G3946S	14	Proband	Syncope	15	No	No	34	Nadolol 160 (2.7)	Couplets	200 (3.3)	18	Complete	No
22	Female	R420Q	14	Proband	Syncope	15	No	Yes	20	Bisoprolol 1.25 (0.03)	Couplets	200 (4.0)	17	No	No
23‡	Female	R2474G	1	Proband	Convulsion without fever	11	No	Yes	18	Atenolol 100 (2.1) Verapamil 120 (2.6)	NSVT	150 (3.2)	20	Complete	No
24	Female	R420W	NA	Relative	None	20	Yes	No	24	Metoprolol 25 (0.4)**	Bigeminy/ frequent VPBs + side effects	100 (1.8)	17	Complete	No
25	Female	E1724K	10	Proband	Syncope	31	No	No	39	Carvedilol 2.5 (0.05)	NSVT	100 (2.2)	14	Partial	No
26‡	Female	F2215L	5	Proband	Cardiac arrest	10	Yes	No	24	Propranolol 140 (2.8)	NSVT (on Holter recordings) + syncope + palpitations	100 (2.0)	13	No	No
27	Female	R4157H	56	Relative	Palpitations	57	No	Yes	57	Bisoprolol 5 (0.08)††	NSVT	150 (2.3)	31	NA†††	No
28	Female	M3978I	14	Relative	Syncope	15	No	Yes	25	Nadolol 40 (0.7)	Frequent VPBs + syncope	150 (2.5)	31	Complete	Nausea and dizziness
29	Female	M3978I	14	Proband	Syncope	14	No	Yes	26	Bisoprolol 5 (0.06)‡‡	Bigeminy/frequent VPBs	150 (3.1)	32	No	No
30	Female	M3978I	13	Relative	Syncope	32	No	No	45	None§§	Bigeminy/frequent VPBs	150 (2.3)	NA||||	Partial	Nausea and dizziness
31	Female	M3978I	13	Relative	Syncope	38	No	No	50	Bisoprolol 5 (0.09)	VPBs + palpitations	100 (1.8)	NA##	No	Nausea and dizziness
32	Male	V4771I	4	Proband	Syncope with seizure	18	No	No	18	Sotalol 240 (3.2)	NSVT	200 (2.7)	29 years***	Complete	No
33‡	Female	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	No
Total	Female: 23 (70%)	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%) Ca²⁺ 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 one 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 three consecutive pregnancies, and thereafter agreed with her treating cardiologist to persistently 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 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 as compared with the baseline exercise test on 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 on β-blocker and flecainide was performed.

***
This patient was excluded from the follow-up calculation.

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

Table 2

Exercise test results at the baseline exercise test on standard therapy and at the first exercise test on the final (stable) flecainide dose

Variable	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 per minute	57±10	59±9	0.061
Sinus rate at maximal exercise, beats per minute	145±23	133±18	0.002
Maximum workload attained, METS	11±3	12±4	0.042
Sinus rate at onset of ventricular arrhythmias, beats per minute	113±19	118±19	0.046 [*]
Maximum number of VPBs during a 10-seconds period [†]	12±5	5±5	<0.001
Ratio of VPBs to sinus beats during the 10-seconds period with the maximum number 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 per minute)	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 ± standard deviation, median (range), or n (%).

[*] Only the 22 patients who still had ventricular ectopy at the first exercise test on the stable flecainide dose were included in this analysis.

[†] Data were available for 28 patients (not available in patient #32).

METS = metabolic equivalents; VPB = ventricular premature beat; NSVT = nonsustained ventricular tachycardia.