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Published in final edited form as:

Title: Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia.

Authors: Watanabe H, van der Werf C, Roses-Noguer F, Adler A, Sumitomo N, Veltmann C, Rosso R, Bhuiyan ZA, Bikker H, Kannankeril PJ, Horie M, Minamino T, Viskin S, Knollmann BC, Till J, Wilde AA

Journal: Heart rhythm : the official journal of the Heart Rhythm Society

Year: 2013 Apr

Volume: 10

Issue: 4

Pages: 542-7

DOI: 10.1016/j.hrthm.2012.12.035

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Published in final edited form as:

Heart Rhythm. 2013 April ; 10(4): . doi:10.1016/j.hrthm.2012.12.035.

Effects of Flecainide on Exercise-Induced Ventricular Arrhythmias and Recurrences in Genotype-Negative Patients with Catecholaminergic Polymorphic Ventricular Tachycardia

Hiroshi Watanabe, MD, PhD, FESC¹, Christian van der Werf, MD², Ferran Roses-Noguer, MD³, Arnon Adler, MD⁴, Naokata Sumitomo, MD⁵, Christian Veltmann, MD⁶, Raphael Rosso, MD⁴, Zahurul A. Bhuiyan, MD, PhD⁷, Hennie Bikker, PhD⁸, Prince J. Kannankeril, MD, MSCI⁹, Minoru Horie, MD, PhD¹⁰, Tohru Minamino, MD, PhD¹, Sami Viskin, MD⁴, Björn C. Knollmann, MD, PhD¹¹, Jan Till, MD³, and Arthur A.M. Wilde, MD, PhD²

¹Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan ²Heart Failure Research Center, Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands ³Department of Paediatric Cardiology, Royal Brompton Hospital, London, UK ⁴Department of Cardiology, Tel Aviv Sourasky Medical Center, Sackler School of Medicine, Tel Aviv University, Israel ⁵Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan ⁶First Department of Medicine, University Medical Centre Mannheim, Mannheim, Germany ⁷Laboratoire de Génétique Moléculaire, Service de Génétique Médicale, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland ⁸Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands ⁹Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA ¹⁰Department of Cardiovascular and Respiratory Medicine Department of Family Medicine, Shiga University of Medical Science, Otsu, Japan ¹¹Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Abstract

Background—Conventional therapy with β -blockers is incompletely effective in preventing arrhythmic events in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). We have previously discovered that flecainide in addition to conventional drug therapy prevents ventricular arrhythmias in genotype-positive CPVT patients.

Objective—To study the efficacy of flecainide in genotype-negative CPVT patients.

Methods—We studied the efficacy of flecainide for reducing ventricular arrhythmias during exercise testing and preventing arrhythmia events during long-term follow-up.

Results—Twelve genotype-negative CPVT patients were treated with flecainide. Conventional therapy failed to control ventricular arrhythmias in all patients. Flecainide was initiated because of significant ventricular arrhythmias (n=8), syncope (n=3), or cardiac arrest (n=1). At the baseline exercise test before flecainide, 6 patients had ventricular tachycardia and 5 patients had bigeminal or frequent ventricular premature beats. Flecainide reduced ventricular arrhythmias at the exercise test in 8 patients compared to conventional therapy, similarly to genotype-positive patients in our previous report. Notably, flecainide completely prevented ventricular arrhythmias in 7 of the

Corresponding Author: Arthur A.M. Wilde, MD, PhD, Academic Medical Center, University of Amsterdam, Department of Cardiology, Heart Failure Research Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Phone: +31-(0)205663072. Fax.: +31-(0)206962609. a.a.wilde@amc.uva.nl.

Disclosures: None declared

patients. Flecainide was continued in all patients except for one who had ventricular tachycardia at the exercise test on flecainide. During a follow-up of 48±94 months, arrhythmia events (sudden cardiac death and aborted cardiac arrest) associated with noncompliance occurred in two patients. Flecainide was not discontinued due to side effects in any of the patients.

Conclusion—Flecainide was effective in genotype-negative CPVT patients, suggesting that spontaneous Ca²⁺ release from ryanodine channels plays a role in arrhythmia susceptibility, similarly to genotype-positive patients.

Keywords

catecholaminergic polymorphic ventricular tachycardia; arrhythmia; sudden death; genetics; antiarrhythmic drugs; flecainide; beta-blockers

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by bidirectional or polymorphic VT induced by adrenergic stress in the absence of structural heart disease.¹⁻³ Three causative genes have been identified for CPVT: *RYR2*, which encodes the cardiac ryanodine receptor Ca²⁺ release channel, *CASQ2*, which encodes cardiac calsequestrin, and *TRDN*, which encodes triadin, and all of them are constitutive proteins of the macromolecular Ca²⁺ release complex in the sarcoplasmic reticulum.⁴⁻⁷ A mutation in these genes is identified in approximately 60-70% of patients with CPVT.^{2, 8} A locus on chromosome 7p14-p22 has also been linked to CPVT, but a corresponding gene has not been identified yet.⁹ Furthermore, mutations in *KCNJ2* encoding the potassium inwardly-rectifying channel Kir2.1, which generally are associated with Andersen-Tawil syndrome, may phenocopy CPVT.¹⁰

Treatment with β -adrenergic blockers reduces ventricular arrhythmia burden and mortality in patients with CPVT. However, the efficacy of β -blockers is not sufficiently protective and an estimated 8-year rate of fatal or near-fatal events on β -blocker therapy is 15%.^{2, 3} Although the beneficial effects of the calcium channel blocker verapamil in combination with a β -blocker have been reported,¹¹⁻¹⁴ the role of verapamil has not been well assessed.² Left cardiac sympathetic denervation has been reported to be highly effective in severely affected patients, but requires surgery and is not universally available.¹⁵ Implantable cardioverter defibrillators (ICDs) are recommended for prevention of sudden death in patients with CPVT.¹⁶ However, painful shocks can trigger further adrenergic stress and arrhythmias, and deaths have occurred despite appropriate ICD shocks.^{17, 18} We have recently discovered that the antiarrhythmic agent flecainide inhibits Ca²⁺ release from ryanodine receptor¹⁹ and that flecainide in addition to conventional drug therapy prevents ventricular arrhythmias in CPVT patients carrying a mutation in *RYR2* or *CASQ2*.³ Here, we studied the efficacy and safety of flecainide in CPVT patients with no mutations in *RYR2*, *CASQ2* and *KCNJ2*, who have similar risk of arrhythmia events to genotype-positive patients.²

Methods

Study population

This study included all consecutive genotype-negative CPVT patients in whom flecainide was started because of the insufficient efficacy of conventional therapy with β -blockers \pm verapamil at 5 tertiary referral centers in the Netherlands, the United Kingdom, Israel, Japan, and Germany. All patients had a clinical diagnosis of CPVT based on adrenergic stress-induced bidirectional or polymorphic VT in the absence of structural heart abnormalities by

echocardiography.²⁰ All families received genetic counseling and all investigated individuals consented to both cardiologic evaluation and genetic testing. Patients were screened for a putative pathogenic mutation in all exons of *RYR2*, *CASQ2*, and *KCNJ2*. Only individuals who were not carrying proven or putative pathogenic mutations in all of these genes were included. Decisions on administration of flecainide and its dose were made by the local cardiologists. Data collection and analysis were done retrospectively by chart review. Patients in whom the dose of β -blocker or verapamil was increased after the initiation of flecainide were not included in this study.

Outcome measures

The efficacy of flecainide on CPVT was compared between the last exercise test on conventional therapy and the first exercise test on a stable dose of flecainide after 5 days of the initiation. Exercise testing was performed using treadmill (standard or modified Bruce protocols) or bicycle ergometer depending on the institutions. Ventricular arrhythmias during exercise testing were quantified using the ventricular arrhythmia score defined by the worst ventricular arrhythmia observed: 1=no or isolated ventricular premature beats (VPBs), 2=bigeminal VPBs and/or >10 VPBs per minute, 3=couplet, 4=NSVT.²⁰ In addition, the presence of either of the parameters of the ventricular arrhythmia score, sinus rate at the onset of ventricular ectopy, most often an isolated VPB, the maximum number of VPBs during a 10-second period, and the ratio of VPBs/sinus beats during the 10-second period with the maximum number of VPBs were analyzed. The effects of flecainide on arrhythmic events including syncope, aborted cardiac arrest, appropriate ICD shocks, and sudden cardiac death during follow-up were also assessed.

Data analysis

Values are expressed as mean \pm SD. To study the effects of flecainide during exercise testing, related data were compared using paired Wilcoxon signed-rank test for continuous and ordinal variables and McNemar test for dichotomous variables. All statistical analyses were performed with SPSS, version 20.0 (SPSS Inc., Chicago, IL). A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

We identified 12 genotype-negative CPVT patients who received flecainide (Table 1). Mean age at baseline was 22 \pm 11 years and 6 patients were female. Our cohort included 7 patients with a family history of CPVT (6 probands and 1 family member). Nine patients had a history of syncope and/or cardiac arrest. In patient #6, a common variant of unknown significance (VUS), p.Val507Ile, was identified in *RYR2*. Patient #11 tested heterozygote positive for two new VUS in *CASQ2*: c.158G>T (p.Cys53Phe) and c.838+3A>G. The c.158G>T VUS was once detected in 13000 control alleles, whereas the c.838+3A>G may affect splicing at the donorsite of exon 8 and was not detected in 13000 control alleles. Before the initiation of flecainide, β -blockers failed to suppress ventricular arrhythmias in all patients. In 7 patients, multiple drugs including β -blockers, verapamil, and other antiarrhythmic drugs failed to suppress ventricular arrhythmias before flecainide was initiated.

Effects of flecainide on exercise-induced ventricular arrhythmias

Among genotype-negative patients, 6 patients (50%) had VT and 5 patients (42%) had couplet or bigeminal VPBs at the baseline exercise testing before flecainide administration (Tables 1 and 2). In a remaining patient who had syncope during a combination therapy with

propranolol and verapamil (patient #3), there was no ventricular arrhythmia during the baseline exercise testing. Flecainide improved the ventricular arrhythmia score at exercise testing in 8 patients (67%) compared to that during conventional therapy (Figure), while the maximum workload during flecainide therapy was increased compared to that during conventional drug therapy (Table 2). The effects of flecainide seemed similar to that in genotype-positive patients in our previously report (76%).²⁰ Flecainide completely suppressed ventricular arrhythmias in 7 patients (58%) and suppressed VT in 4 of the 6 patients who developed VT during the baseline testing. Compared to the baseline exercise test, flecainide reduced the maximum number of VPBs during a 10-seconds period. In one patient (patient #10), flecainide was discontinued because of VT during exercise testing.

Effects of flecainide on arrhythmia events

A total of 11 patients (92%) continued to receive flecainide and were included in the further analysis of the incidence of arrhythmic events. During a mean follow-up of 48±94 months, arrhythmia events associated with noncompliance occurred in 2 of 11 genotype-negative patients. Patients #6 died suddenly while playing soccer. Although flecainide combined with nadolol suppressed ventricular tachycardias during exercise testing, the patient self-discontinued the drug therapy after his last visit to the clinic. Patient #1 collapsed and was resuscitated by his relatives. The patient had not taken flecainide from the night before the collapse, and the serum level of flecainide was low (0.13 mg/L; therapeutic range, 0.4-0.9 mg/L) at the event. Metoprolol and flecainide were resumed at the previous doses, and no event occurred thereafter. In the remaining 9 patients, there was no arrhythmia event during the follow-up period, while 7 of the 9 patients had arrhythmia events despite conventional drug therapy before the initiation of flecainide. Flecainide was not discontinued due to side effect in any of the patients.

Discussion

In this study, flecainide suppressed ventricular arrhythmias during exercise testing in genotype-negative patients similar to genotype-positive CPVT patients. Flecainide was highly effective in preventing arrhythmia events during a long-term follow-up.

CPVT has been associated with mutations in *RYR2*, *CASQ2*, and *TRDN*.⁴⁻⁷ Mutations in these genes destabilize the ryanodine channel complex in the sarcoplasmic reticulum and result in spontaneous Ca²⁺ release through the ryanodine channel leading to delayed after depolarizations, triggered activity, and VT.²¹⁻²⁴ Recently, we and others have identified the therapeutic effects of flecainide in CPVT.^{19, 25, 26} Flecainide directly inhibits the ryanodine channel and suppresses delayed afterdepolarizations and triggered activity in mutant cardiomyocytes in which *Ryr2* or *Casq2* loci are modified.^{19, 26, 27} In our mouse model of CPVT, flecainide prevents spontaneous VT and inducible VT by exercise or isoproterenol.¹⁹ Yet, we have recently discovered that flecainide prevents CPVT in patients carrying a mutation in *RYR2* or *CASQ2*, possibly resulting in spontaneous Ca²⁺ release.^{19, 20} In this study, flecainide was also effective in genotype-negative CPVT patients, similarly in genotype-positive patients in our prior study.²⁰ Notably, all arrhythmia events during flecainide therapy were associated with noncompliance in our present and prior studies.²⁰

The efficacy of flecainide in genotype-negative CPVT patients suggests that uncontrolled Ca²⁺ release through the ryanodine channel is also important as the underlying mechanisms in patients without an identified mutation in *RYR2* or *CASQ2*, that account for 30-40% of patients with CPVT.^{3, 28} There are a certain number of CPVT patients with positive family history but negative genotyping results, suggesting the presence of other causative genes that have not been identified yet. Unknown genetic backgrounds of CPVT may include genes encoding the constitutive proteins and the modifiers of macromolecular Ca²⁺ release

complex. For example, homozygosity for mutations in *TRDN* encoding triadin, an anchoring protein of calsequestrin to ryanodine channel, has very recently been identified in families affected by CPVT.⁷ Furthermore, flecainide may suppress CPVT through sodium channel blocking effects as we and others have previously proposed.^{19, 26}

Genotype-phenotype correlations have been studied in inherited arrhythmia syndromes. The genotype contributes to risk stratification and impacts on therapeutic decisions in long QT syndrome; the most studied arrhythmia syndrome.²⁹ In CPVT, the risk of arrhythmia events and the efficacy of β -blocker seem to be similar in genotype-positive and genotype-negative patients.² Our findings indicate that flecainide can be used regardless of genotyping results in CPVT patients in whom β -blockers fail to control their ventricular arrhythmias or symptoms.

Our study has several limitations. The number of patients was limited because CPVT is a very rare disease. Therefore, the efficacy of flecainide could not be systematically assessed and further studies, probably randomized controlled studies, are needed.³⁰ Patients with CPVT whose arrhythmias are refractory to the conventional drug therapy were included in this study and our previous study.²⁰ Therefore, the efficacy of flecainide in patients whose arrhythmias are well responded to the conventional therapy is not known. Exercise testing is used to assess the effects of therapies in CPVT and our previous study showed that ventricular arrhythmia scores at exercise testing are reproducible measures of drug efficacy in CPVT.²⁰ However, the predictive ability of ventricular arrhythmia scores for arrhythmia events is not clear. Finally, the patients in this study were not tested for mutations in *TRDN*.⁷ However, in this study, none of the patients were from a consanguineous family, so the possibility of identifying mutations in *TRDN* seems very low.

In conclusion, we found that flecainide was effective in suppressing ventricular arrhythmias during exercise and preventing arrhythmia events in genotype-negative CPVT patients, similarly to genotype-positive patients. Our results suggest that flecainide can be added, regardless of genotype, to control ventricular arrhythmias or symptoms, when they are insufficiently controlled by conventional therapy with β -blockers.

Acknowledgments

This work was supported by a grant from Ministry of Education, Culture, Sports, Science and Technology, Japan (2012-24591038) (HW), by ZorgOnderzoek Nederland Medische Wetenschappen (ZonMW, grant 120610013 to C.W. and A.A.M.W.), and in part by NIH grant R01HL88635 (BCK) and American Heart Association Established Investigator Award 0840071N (BCK).

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Abbreviations

CPVT	catecholaminergic polymorphic ventricular tachycardia
ICD	implantable cardioverter defibrillators
NSVT	non-sustained ventricular tachycardia
VPB	ventricular premature beats

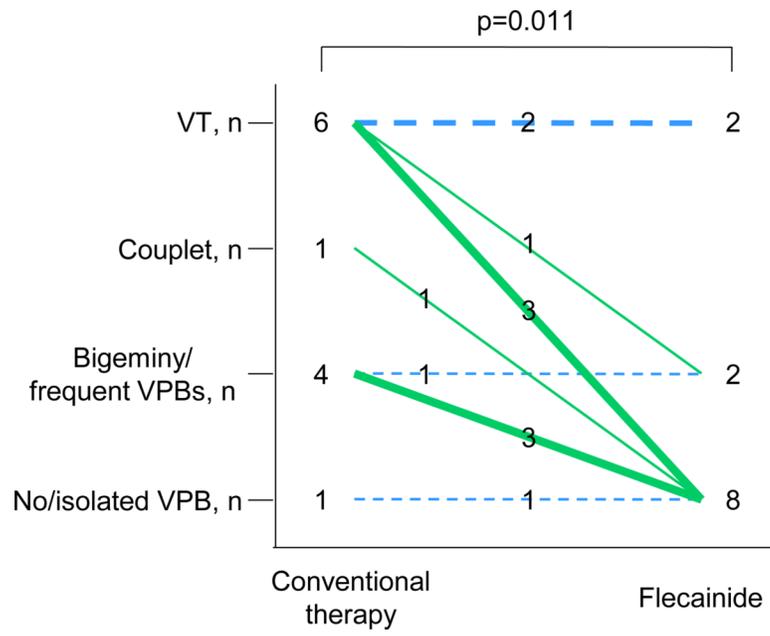


Figure. Effects of flecainide on exercise-induced ventricular arrhythmias. Ventricular arrhythmias during exercise testing were compared between conventional therapy and flecainide in genotype-negative patients. Green line indicates suppression of ventricular arrhythmias by flecainide; blue line, no change. VT denotes ventricular tachycardia; VPB, ventricular premature beat.

Table 1

Characteristics of genotype-negative CPVT patients who received flecainide

Patient No.	Sex	Age at onset, years	Family history		Cardiac arrest	Presenting symptom	Negative gene	Age at baseline, years	Drug therapy at baseline exercise test, mg (mg/kg body weight)	Indication for flecainide	Flecainide dose, mg (mg/kg body weight)	Baseline exercise test		Effects of flecainide	
			Sudden death	CPVT								Exercise test	Follow-up, months	Arrhythmia events	Side effects*
1	M	7	No	No	Yes	RYR2, CASQ2, KCNJ2	15	Metoprolol 200 (3.4)	Cardiac arrest	200 (3.4)	Bigeminal VPBs	Bigeminal VPBs	328	Yes [‡]	No
2	F	12	No	Yes	Yes	RYR2, CASQ2, KCNJ2	31	Metoprolol 400 (4.7), Verapamil 240 (2.8)	Bigeminal/frequent VPBs	200 (2.4)	Bigeminal VPBs	Bigeminal VPBs	41	No	No
3	M	6	No	Yes	No	RYR2, CASQ2, KCNJ2	9	Propranolol 160 (2.3), Verapamil 120 (1.7)	Syncope	150 (2.1)	No arrhythmia	Isolated VPBs	41	No	No
4	F	8	Yes	Yes	No	RYR2, CASQ2, KCNJ2	15	Propranolol 120 (3.0), Verapamil 120 (3.0)	VT	100 (2.5)	Bigeminal VPBs	No arrhythmia	41	No	No
5	F	15	No	No	Yes	RYR2, CASQ2, KCNJ2	35	Metoprolol 100 (2.0)	Cardiac arrest	VT	100 (2.0)	VT	34	No	No
6	M	10	Yes	Yes	No	RYR2, CASQ2, KCNJ2	21	Nadolol 120 (2.1)	Syncope	Syncope	150 (2.7)	VT	4	Yes [‡]	No
7	F	40	Yes	Yes	No	RYR2, CASQ2, KCNJ2	43	Nadolol 20 (0.2) [‡]	Palpitation	VT	200 (2.0)	VT	18	No	No
8	M	11	Yes	Yes	No	RYR2, CASQ2, KCNJ2	20	Propranolol 80 (1.8)	None (positive family history)	VT during exercise testing	150 (3.3)	VT	6	No	No
9	M	16	No	No	No	RYR2, CASQ2, KCNJ2	19	Bisoprolol 10 (0.13)	Cardiac arrest	VT	100 (1.3)	Bigeminal VPBs	8	No	No
10	F	10	No	Yes	No	RYR2, CASQ2, KCNJ2	15	Nadolol 120 (2.1), Bisoprolol 10 (0.18)	Syncope	VT during exercise testing	200 (3.6)	VT	Discontinued after exercise testing	No	No
11	M	9	No	No	No	RYR2, CASQ2, KCNJ2	11	Nadolol 80 (2.3)	Syncope	Syncope	225 (6.5)	Couplet VPBs	5	No	No
12	F	39	No	No	No	RYR2, CASQ2, KCNJ2	39	Bisoprolol 5 (0.07)	Palpitation	VT	200 (2.9)	VT	7	No	No
Total	M: 6	15±11	Yes: 4 (33%)	Yes: 7 (58%)	Symptoms: 11 (92%)	RYR2: 12 (100%), CASQ2: 12 (100%), KCNJ2: 12 (100%)	22±11	-blocker: 12 (100%), Verapamil: 3 (25%)	VT: 8 (67%)	165±46 (2.9±1.3)	VT: 6 (50%)	VT: 2 (17%)	48±94	Yes: 2 (17%)	Yes: 0 (0%)

CPVT denotes catecholaminergic polymorphic ventricular tachycardia; VPB, ventricular premature beat.

* Side effects requiring discontinuation of flecainide.

[‡] Episode occurred after noncompliance of flecainide.

[‡] The patient could not tolerate larger dose.

Table 2
Effects of flecainide on ventricular arrhythmias during exercise testing

	Standard therapy	Flecainide	P-value
Sinus rate at baseline, beats/min	68±14	72±28	0.82
Sinus rate at maximal exercise, beats/min	148±26	136±23	0.33
Maximum workload attained, METs	9±3	11±3	0.19
Sinus rate at onset of ventricular arrhythmias, beats/min	114±34	117±23	0.50
Maximum no. of VPBs during a 10 seconds	12±7	6±7	0.02
Ratio of VPBs to sinus beats during 10 seconds with the maximum no. of VPBs	1.5±2.6	0.5±0.6	0.21
Isolated VPB	11 (92)	6 (50)	0.03
Bigeminal VPBs	10 (83)	5 (42)	0.03
Frequent VPBs (>10/min)	9 (75)	5 (42)	0.10
Couplet	8 (67)	3 (25)	0.10
Nonsustained ventricular tachycardia	6 (50)	2 (17)	0.10
Longest ventricular salvo, VPBs	9.5 (3-16)	5 (4-6)	0.13
Bidirectional NSVT	4 (33)	1 (8)	0.08

Values are mean±SD or number (%).