Journal of Cardiology Cases 11 (2015) 10–13

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

High-dose flecainide with low-dose β-blocker therapy in catecholaminergic polymorphic ventricular tachycardia: A case report and review of the literature

Johannes Steinfurt (MD)[a], Markus-Johann Dechant (MD)[b], Doris Böckelmann[c], Sven Zumhagen (MD)[c], Brigitte Stiller (MD, PhD)[b], Eric Schulze-Bahr (MD, PhD)[c], Christoph Bode (MD)[a], Katja E. Odening (MD)[a,*]

[a] Department of Cardiology and Angiology I, Heart Center, University of Freiburg, Freiburg, Germany
[b] Department of Congenital Heart Defects and Paediatric Cardiology, Heart Center, University of Freiburg, Freiburg, Germany
[c] Institute for Genetics of Heart Diseases (IfGH), Department of Cardiovascular Medicine, University Hospital Münster, Münster, Germany

ARTICLE INFO

Article history:
Received 18 July 2014
Received in revised form 9 August 2014
Accepted 23 August 2014

Keywords:
Catecholaminergic polymorphic ventricular tachycardia
Beta blocker
Compliance
Flecainide
Sudden cardiac death

ABSTRACT

Background: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by recurrent syncopes and sudden cardiac death triggered by sympathetic activation in young individuals without structural heart disease and a normal baseline electrocardiogram. There is reason to question whether the current expert consensus treatment recommendation, *maximal* tolerated β-blockade alone or in combination with low-dose flecainide, is the *optimal* antiarrhythmic treatment strategy in CPVT, as high doses of β-blockers may eventually lead to adverse side effects and β-blocker discontinuation. Indeed, β-blocker non-compliance accounts for around 5% of sudden cardiac deaths in CPVT patients.
Case report: Differing from the current recommendation, we present the first report of a CPVT patient successfully treated with high-dose flecainide and *minimal* β-blockade. This combination resulted in complete suppression of ventricular arrhythmias during exercise stress tests and Holter monitoring and was well tolerated without any side effects. We review the current literature on β-blocker non-compliance-related sudden cardiac death in CPVT, summarize the *in vitro* and *in vivo* data on flecainide therapy in CPVT, and discuss the rationale of our antiarrhythmic approach.
<**Learning objective:** This case illustrates typical features of CPVT including the therapeutic management of a young CPVT patient with poor β-blocker tolerance at normal dosages. In this setting, high-dose flecainide combined with *minimal* β-blockade may (1) result in complete antiarrhythmic response and may (2) improve the antiarrhythmic drug-compliance thereby reducing the risk of non-compliance-related sudden cardiac death.>

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by the occurrence of syncopes and sudden cardiac death (SCD) in young individuals without structural heart disease and a normal baseline electrocardiogram (ECG). Cardiac events are triggered by sympathetic activation during emotional or physical stress [1,2]. In 50–60%, a mutation in the cardiac ryanodine receptor gene (*RYR2*) and an increased adrenergic tone may lead to diastolic calcium release from the sarcoplasmic reticulum through the defective (“leaky”) RYR2 channels, a cytosolic calcium overload, subsequent delayed after-depolarizations (DADs), and triggered activity, manifesting as ectopic beats, bigeminy, and polymorphic or bidirectional ventricular tachycardia, the hallmark of CPVT [1–3].

Since 2013, flecainide has been included in the pharmacological management of CPVT patients [4]. Flecainide appears to have RYR2 blocking properties, thus allowing direct targeting of ‘the molecular defect’ in CPVT [5,6]. In a retrospective analysis of 33 CPVT patient histories, flecainide in combination with standard (mostly high-dose) β-blocker therapy has shown partial or complete antiarrhythmic response in CPVT patients carrying *RYR2* or calsequestrin mutations [7]. Flecainide is now added on

* Corresponding author at: Department of Cardiology and Angiology I, Heart Center, University of Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany. Tel.: +49 761 270 32470; fax: +49 761 270 73090.
E-mail address: katja.odening@universitaets-herzzentrum.de (K.E. Odening).

http://dx.doi.org/10.1016/j.jccase.2014.08.009
1878-5409/

top of an existing standard (*i.e.* maximal tolerated) β-blocker therapy when antiarrhythmic control appears to be incomplete [4]. However, high doses of β-blockers may eventually result in adverse side effects in the course of the disease, leading to β-blocker non-compliance, which accounts for around 5% of SCDs in CPVT. Thus, there is reason to doubt that high-dose β-blockade with addition of flecainide is the *optimal* antiarrhythmic treatment strategy in CPVT.

Case report

A 12-year-old teenager (156 cm, 40 kg) was training in a soccer team at the time of CPVT diagnosis. No stress-related syncope had been noted to date; however, there was a positive family history of SCD. In 2005, one brother (the index patient) died at the age of 14 years during a soccer match due to ventricular fibrillation; he had experienced two episodes of syncope in the past, one while swimming and the second in an emotionally stressful situation at church. In 2011, molecular genetics revealed a novel pathogenic *RYR2* mutation (c. 6647A>C) in four out of six family members (Fig. 1a and b), again prompting clinical evaluation of the family. On exercise testing, the young girl showed polymorphic premature ventricular complexes (PVCs), bigeminy, and couplets. A standard β-blocker therapy with 2.5 mg bisoprolol per day was initiated, but poorly tolerated due to pronounced fatigue, and the patient discontinued the antiarrhythmic therapy for a while. On the next visit, bisoprolol was reduced to a tolerable low dosage of 1.25 mg and combined with flecainide. The antiarrhythmic efficacy of this combination was verified in repetitive exercise stress tests (modified Bruce protocol) and flecainide was increased stepwise to achieve complete antiarrhythmic response (Fig. 2). The lowest flecainide dosage (2 × 50 mg; 2.5 mg/kg body weight per day) (Fig. 2a) could not suppress PVCs on exertion; starting at 165 bpm, sustained ventricular bigeminy, but no couplets, were observed. Increasing flecainide to 2 × 75 mg (3.75 mg/kg body weight per day) (Fig. 2b) reduced ventricular ectopy, and bigeminy occurred only intermittently during the highest workload. On the third exercise stress test (Fig. 2c), a combined treatment with 2 × 100 mg flecainide (5 mg/kg body weight per day) and 1.25 mg bisoprolol showed a complete suppression of catecholaminergic arrhythmias without a single PVC. These findings were confirmed by a 7-day Holter monitoring and at two further follow-up stress tests 6 and 12 months later. The antiarrhythmic therapy was well tolerated with no side effects.

Discussion

Conventional β-blockade has been the established therapy since the first reports of CPVT and the triggering role of sympathetic activation [1,2]. However, β-blocker therapy has a limited efficacy in CPVT, with recurrence rates as high as 30% [2]. Moreover, high doses of β-blockers are associated with adverse side effects and several studies have shown that β-blocker non-compliance accounts for around 5% of SCDs in CPVT (Table 1) [1,2,8–11]. Indeed, skipping just a single β-blocker dose may result in SCD of a CPVT patient [1,2]. Thus, it is critical to have an antiarrhythmic treatment strategy in CPVT that is not only effective, but also well-tolerated.

There is evidence suggesting that flecainide monotherapy may be sufficient to suppress ventricular arrhythmias in CPVT. Flecainide monotherapy resulted in complete suppression of arrhythmias in cell and animal models [5,6,12] and in two CPVT patients without causing any side effects [6,7]. Of note, high flecainide doses of up to 7 mg/kg body weight per day appear to be safe and well-tolerated in infants and children with supraventricular and ventricular tachycardias other than CPVT and no structural heart disease [13]. While β-blockers aim to attenuate the trigger of CPVT, *i.e.* sympathetic activation [3], flecainide acts more specifically and directly targets 'the molecular defect' in CPVT. Two major antiarrhythmic modes of action of flecainide are postulated: (1) a direct blockade of RYR2 channels resulting in a reduced amplitude of DADs [5,14] and (2) a blockade of luminal sodium channels resulting in an increased threshold for triggered activity (with an unaffected DAD

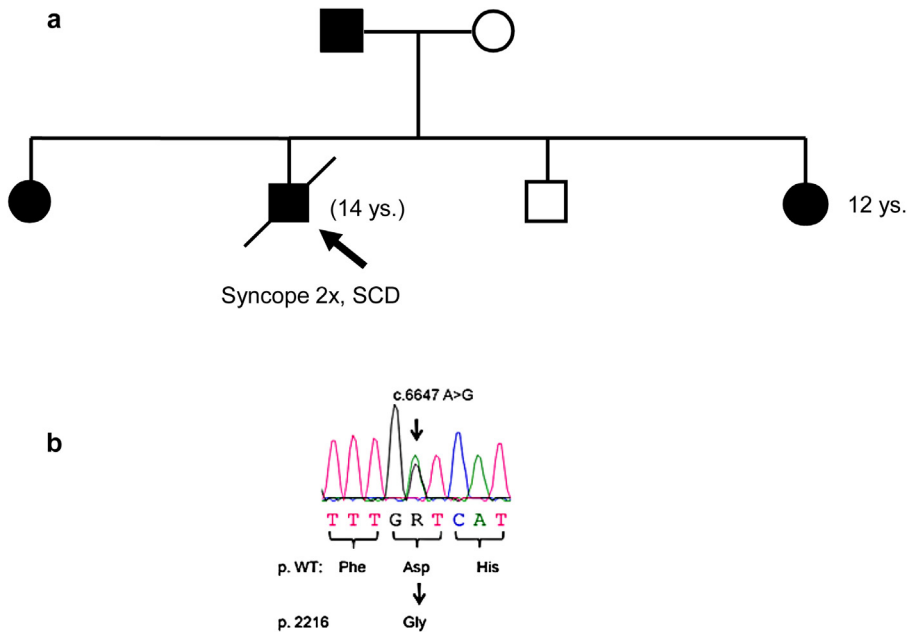

Fig. 1. (a) Pedigree of the affected family carrying the novel *RYR2* mutation (p. Asp2216Gly). Men are denoted by squares and women by circles. Solid symbols indicate mutation carriers, crossed symbols denote deceased patients. The index patient is marked with an arrow. SCD, sudden cardiac death. (b) Electropherogram of the heterozygous *RYR2* mutation c.6647 A>G; an exchange from adenine to guanine leads to the amino acid substitution of aspartate (polar, negatively charged) by glycine (apolar amino acid) at position 2216 in a highly conserved region of the RYR2 protein.

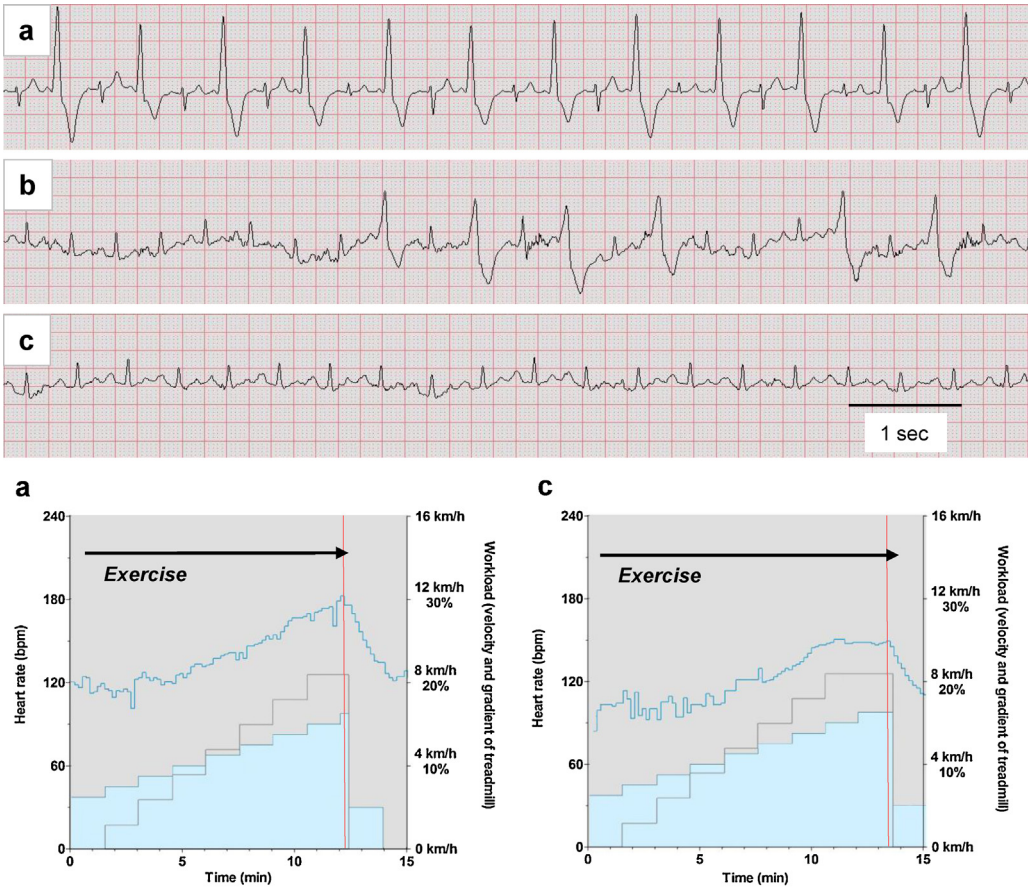

Fig. 2. Exercise electrocardiograms (ECGs) of the young teenager recorded during maximal exertion (treadmill velocity 6.0 km/h at maximal treadmill gradient of 21%) and increasing flecainide dosages from (a) to (c) plus a constant low-dose β-blocker therapy. Vertical lines (red) in the exercise diagrams (bottom) indicate the point when the corresponding ECGs (top) are taken. (a) *Sustained bigeminy* at a heart rate of 182 bpm during maximal exertion and a flecainide dosage of 2.5 mg/kg per day plus 1.25 mg bisoprolol. (b) *Intermittent bigeminy* at a heart rate of 180 bpm during maximal exertion and a flecainide dosage of 3.75 mg/kg per day plus 1.25 mg bisoprolol. (c) *Sinus tachycardia without bigeminy* at a heart rate of 150 bpm during maximal exertion and a flecainide dosage of 5 mg/kg per day plus 1.25 mg bisoprolol. Of note, the arrhythmia suppression improved the patient's exercise capacity allowing her to maintain the highest workload a bit longer.

Table 1 Studies reporting syncopes and SCD related to poor β-blocker compliance in 234 patients with CPVT.

Study (year)	Patients (*n*)	Mean age at diagnosis (years)	Patients on β-blockers	β-Blockers used	Mean follow-up (years)	Syncope or SCD related to β-blocker non-compliance
Leenhardt, 1995 [1]	21	10	100%	Nadolol	7	5%
Lahat, 2001 [8]	13	9	100%	Propranolol	5	8%
Sumitomo, 2003 [9]	29	10	97%	Propranolol	7	3%
Postma, 2005 [10]	54	12	93%	Nadolol Metoprolol Propranolol	2	2%
Celiker, 2009 [11]	16	11	94%	Propranolol	3	6%
Hayashi, 2009 [2]	101	15	80%	Nadolol	8	7%

SCD, sudden cardiac death.

amplitude) [12]. The synergistic mode of action of β-blockers and flecainide favors a combination of both drugs in CPVT; yet the optimal ratio is not clear.

Differing from the current expert recommendation [4], we report the first CPVT patient successfully treated with high-dose flecainide and low-dose β-blockade. We increased flecainide up to 5 mg/kg body weight per day to reach complete antiarrhythmic response and reduced bisoprolol to minimize the incidence of adverse side effects to obtain maximal compliance. Of note, a flecainide dosage of 5 mg/kg body weight per day constitutes the highest flecainide dosage in a CPVT patient with complete antiarrhythmic response reported to date [7].

Conclusions

The current understanding on the synergistic action of β-blockers and flecainide favors a combination of both drugs in CPVT. However, high doses of β-blockers may cause adverse side effects and may lead to non-compliance-related SCD in CPVT patients. In our patient, high-dose flecainide combined with low-dose β-blockade resulted in complete suppression of ventricular arrhythmias during exercise stress tests and Holter monitoring and has been well tolerated without any side effects for more than a year. The optimal ratio of the two drugs in CPVT has yet to be defined.

Conflicts of interest

The authors declare no conflict of interest.

Disclosures

None

References

[1] Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. Circulation 1995;91:1512–9.

[2] Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, Klug D, Takatsuki S, Villain E, Kamblock J, Messali A, Guicheney P, Lunardi J, Leenhardt A. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation 2009;119:2426–34.

[3] Priori SG, Chen SR. Inherited dysfunction of sarcoplasmic reticulum Ca^{2+} handling and arrhythmogenesis. Circ Res 2011;108:871–83.

[4] Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes: Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–63.

[5] Hilliard FA, Steele DS, Laver D, Yang Z, Le Marchand SJ, Chopra N, Piston DW, Huke S, Knollmann BC. Flecainide inhibits arrhythmogenic Ca^{2+} waves by open state block of ryanodine receptor Ca^{2+} release channels and reduction of Ca^{2+} spark mass. J Mol Cell Cardiol 2010;48:293–301.

[6] Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med 2009;15:380–3.

[7] van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, Shimizu W, Sumitomo N, Fish FA, Bhuiyan ZA, Willems AR, van der Veen MJ, Watanabe H, Laborderie J, Haissaguerre M, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol 2011;57:2244–54.

[8] Lahat H, Eldar M, Levy-Nissenbaum E, Bahan T, Friedman E, Khoury A, Lorber A, Kastner DL, Goldman B, Pras E. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p 13-21. Circulation 2001;103:2822–7.

[9] Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, Saito A, Kurosaki K, Jouo K, Koujiro M, Konishi S, Matsuoka S, Oono T, Hayakawa S, Miura M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart 2003;89:66–70.

[10] Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, Dubosq-Bidot L, Sebillon P, Mannens MM, Guicheney P, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. J Med Genet 2005;42:863–70.

[11] Celiker A, Erdogan I, Karagoz T, Ozer S. Clinical experiences of patients with catecholaminergic polymorphic ventricular tachycardia. Cardiol Young 2009;19:45–52.

[12] Liu N, Denegri M, Ruan Y, Avelino-Cruz JE, Perissi A, Negri S, Napolitano C, Coetzee WA, Boyden PA, Priori SG. Short communication: flecainide exerts an antiarrhythmic effect in a mouse model of catecholaminergic polymorphic ventricular tachycardia by increasing the threshold for triggered activity. Circ Res 2011;109:291–5.

[13] Brugada J, Blom N, Sarquella-Brugada G, Blomstrom-Lundqvist C, Deanfield J, Janousek J, Abrams D, Bauersfeld U, Brugada R, Drago F, de Groot N, Happonen JM, Hebe J, Yen Ho S, Marijon E, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace 2013;15:1337–82.

[14] Watanabe H, Steele DS, Knollmann BC. Mechanism of antiarrhythmic effects of flecainide in catecholaminergic polymorphic ventricular tachycardia. Circ Res 2011;109:712–3.