A 35-year effective treatment of catecholaminergic polymorphic ventricular tachycardia with propafenone

Alexandra Marx, MD,* Björn Lange, MD,* Carsten Nalenz, MD,† Boris Hoffmann, MD,* Thomas Rostock, MD,* Torsten Konrad, MD*

*From the *Centre of Cardiology, Department for Cardiology 2, Johannes Gutenberg University Mainz, Mainz, Germany, and †Kardiologie am Gutenberg, Mainz, Germany.*

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inheritable cardiac channelopathy characterized by malignant polymorphic ventricular tachycardias (pVT) that are triggered by catecholaminergic stress.[1,2] Affected patients typically suffer from syncope during physical exercise and/or (aborted) sudden cardiac death within the first 2 life decades.[3] The most common genetic background of the disease is mutations in the gene encoding for the cardiac ryanodine receptor (RyR2).[4]

The first case, of a 6-year-old child with an electrocardiographic pattern of bidirectional ventricular tachycardia and structurally normal heart, was reported in 1975.[1] However, the typical clinical pattern attributed to a distinct electrical heart disease described as catecholaminergic polymorphic ventricular tachycardia was first described in 1995 in a larger series of patients.[2] In this initial series, class I antiarrhythmic drugs were totally ineffective while the beta blocker nadolol effectively suppressed arrhythmias, clinically accompanied by the disappearance of syncope.

We report the case of a patient with an undiagnosed CPVT successfully treated with propafenone for 35 years.

Case report

A 52-year-old male patient presented to our outpatient clinic owing to exercise-induced palpitations. He reported on a history of arrhythmias starting at an age of 14 years. At this time, he suffered from recurrent, exercise-induced syncope. After presentation to several hospitals, an exercise electrocardiogram revealed frequent premature ventricular beats. Subsequently, an antiarrhythmic drug treatment with 150 mg propafenone 3 times per day was initiated. With this medication, recurrent syncope disappeared completely and the patient felt only mild palpitations even with physical activity (including alp sport cycling tours). After 30 years of propafenone treatment with 450 mg/d, the patient reduced the dosage to 300 mg/d at his own decision. With this reduced dose, palpitations during exercise again became more intensive. No side effects of the long-term propafenone treatment were reported by the patient (neither with 450 mg/d nor with 300 mg/d).

The patient's cousin (related by the patient's father) suffered from sudden cardiac death at the age of 35 years. This death was not further investigated but he had no prior history of any diseases. The father of the patient had no history of cardiac diseases and did not suffer from palpitations or syncope. The patient does not have his own children.

The resting 12-lead electrocardiogram of the patient was inconspicuous, with only mild slurring of the terminal QRS complex in the inferior leads (Figure 1). Exercise testing revealed frequent polymorphic premature ventricular beats consistent with bidirectional ventricular arrhythmias (Figure 2). Genetic testing confirmed a pathogenic mutation in the *RyR2* gene (c.1259G>A; p.Arg420Gln). This mutation was previously reported to be associated with CPVT.[5] To date, there are 13 families known with 29 carriers and phenotypical CPVT. The mutation is not found in healthy controls and functional studies showed an effect on the ryanodine receptor with markedly increased calcium current.[6] Cascade screening of first-degree relatives was recommended.

We initiated a treatment with propranolol (160 mg/d) in addition to propafenone 300 mg/d (nadolol has limited availability in Germany). During exercise test with this medication, only rare premature ventricular contractions occurred (Figure 3). Thus, propranolol had a clear additive effect to propafenone 300 mg/d in this patient. Until now, the patient did not suffer again from syncope or documented sustained ventricular arrhythmias. Since the patient was free of syncope under the treatment of propafenone alone and under combined therapy with propranolol free

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Address reprint requests and correspondence: Dr Alexandra Marx, University of Mainz, Center of Cardiology, Clinic of Cardiology II, Electrophysiology, Langenbeckstr. 1, 55131 Mainz, Germany. E-mail address: alexandra.marx@unimedizin-mainz.de.

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KEY TEACHING POINTS

- Despite proven catecholaminergic polymorphic ventricular tachycardia (CPVT) with pathogen RyR2 mutation and recurrent syncope, patients could have a favorable long-term outcome over 35 years under treatment.
- Propafenone could be effective for treatment of patients with CPVT.
- The beneficial effect of the monotherapy with propafenone in our patient may result from the combined antiarrhythmic effect of this drug with Na^+ channel blockade and beta blocker capabilities.

of pVTs, an implantable cardioverter-defibrillator implantation was not performed.

Discussion

We report the case of a patient with a *RyR2* gene mutation–associated CPVT that has been successfully treated with propafenone for 35 years. Of note, this treatment has been initiated as an ex juvantibus therapy 15 years before this disease was first described systematically and implemented as a distinct arrhythmogenic disorder in 1995. Although class I antiarrhythmic drugs were described to be ineffective in the initial series, flecainide has been proven to be effective in CPVT in further studies.[7] Therefore, according to the current Heart Rhythm Society consensus statement, flecanide treatment is recommended in certain cases in combination with beta blocker therapy.[8] An implantable cardioverter-defibrillator implantation is only recommended in CPVT patients who experience cardiac arrest, recurrent syncope, or sustained pVT despite optimal medical management.[8] As an alternative, left cardiac sympathetic denervation has also been proven to be effective.[9]

Sodium channel blockade leads to a reduced occurrence of triggered activity.[10] In an experimental mouse model, flecainide was able to reduce Ca^{2+}; the same effect has been described for propafenone.[11] However, all existing studies with flecainide were done in combination with beta blocker therapy. The beneficial effect of the monotherapy with propafenone in our patient may result from the combined antiarrhythmic effect of this drug with Na^+ channel blockade and beta blocker capabilities as well as other, possibly unknown pharmacologic properties.[12] Even though larger studies are required, this case shows that propafenone may be an interesting therapeutic option for patients with CPVT.

Conclusion

With the presented case report, we describe the effectiveness of a monotherapy with propafenone over a follow-up period of 35 years. To the best of our knowledge, this is the longest follow-up reported in a patient with CPVT. Since

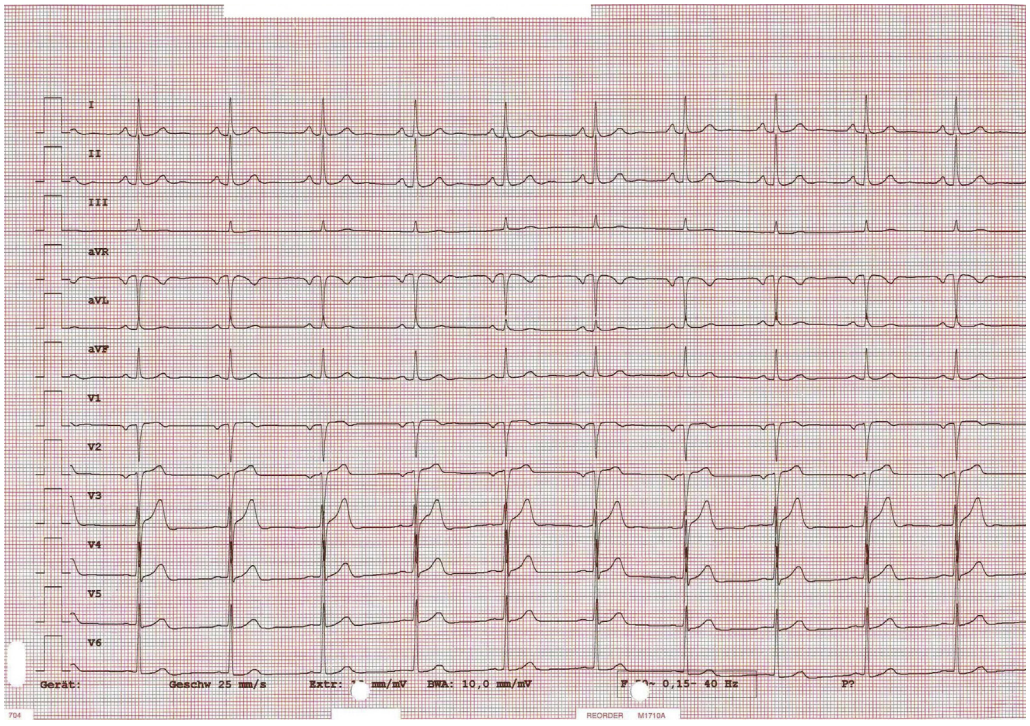

Figure 1 Resting electrocardiogram of the patient.

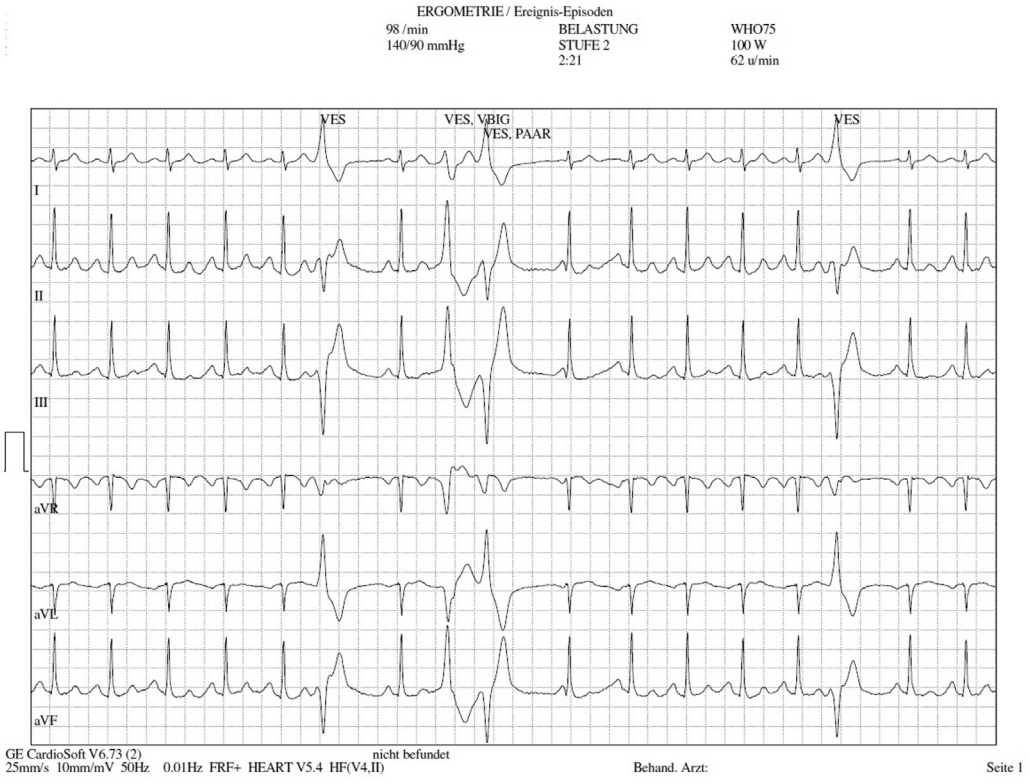

Figure 2 Exercise stress test at 125 W level showing multiple premature ventricular contractions and 1 bidirectional couplet, paper speed 25 mm/s.

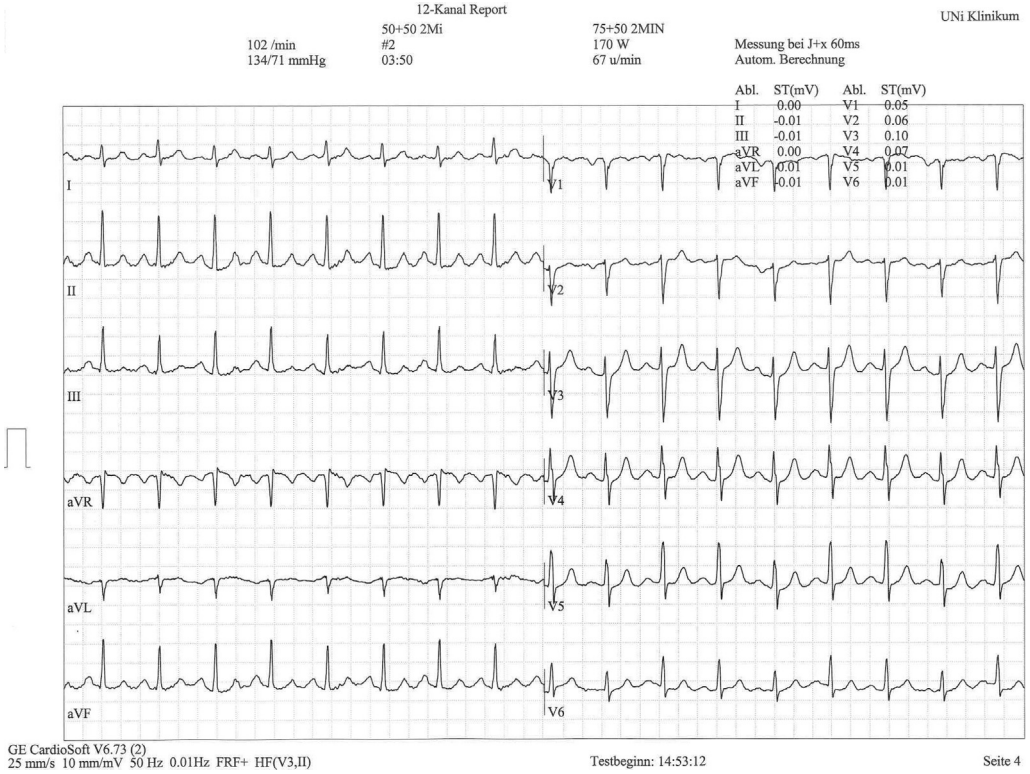

Figure 3 Exercise stress at 170 W level under 300 mg propafenone + 160 mg propranolol per day without any premature ventricular contractions.

propafenone harbors potentially the ideal antiarrhythmic features of a drug for the treatment of CPVT, further studies in larger series of CPVT patients are desired to prove the effectiveness of propafenone in this distinct arrhythmogenic disease.

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