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

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\section*{Abstract}

\textbf{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 (ECG). There is reason to question whether the current expert consensus treatment recommendation, \textit{maximal} tolerated β-blockade alone or in combination with low-dose flecainide, is the \textit{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.

\textbf{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.

\textbf{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.

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\section*{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
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
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].

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Mean age at diagnosis (years)</th>
<th>Patients on β-blockers</th>
<th>β-Blockers used</th>
<th>Mean follow-up (years)</th>
<th>Syncope or SCD related to β-blocker non-compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leenhardt, 1995 [1]</td>
<td>21</td>
<td>10</td>
<td>100%</td>
<td>Nadolol</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Lahat, 2001 [8]</td>
<td>13</td>
<td>9</td>
<td>100%</td>
<td>Propranolol</td>
<td>5</td>
<td>8%</td>
</tr>
<tr>
<td>Sumitomo, 2003 [9]</td>
<td>29</td>
<td>10</td>
<td>97%</td>
<td>Propranolol</td>
<td>7</td>
<td>3%</td>
</tr>
<tr>
<td>Postma, 2005 [10]</td>
<td>54</td>
<td>12</td>
<td>93%</td>
<td>Nadolol</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metoprolol</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayashi, 2009 [2]</td>
<td>101</td>
<td>15</td>
<td>80%</td>
<td>Nadolol</td>
<td>8</td>
<td>7%</td>
</tr>
</tbody>
</table>

SCD, sudden cardiac death.

**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