Successful treatment of catecholaminergic polymorphic ventricular tachycardia with flecainide: a case report and review of the current literature

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disease that can cause sudden cardiac death due to ventricular fibrillation (VF). While pharmacological therapy with beta-blockers and/or Ca2+ antagonists is often unreliable, a recent study has demonstrated that flecainide can effectively suppress arrhythmia in a murine model of CPVT as well as clinically in two human subjects suffering from CPVT. We here present the case of an 11-year-old boy suffering from CPVT-1 as well as a review of the current relevant literature. After resuscitation due to VF at age 9, an automated implantable cardioverter–defibrillator (ICD) was implanted in 2007. Under beta-blocker therapy, repeated shocks were delivered due to either fast ventricular tachycardia (VT) or VF. This persisted under additional therapy with verapamil. Implantable cardioverter–defibrillator routine interrogations showed frequent non-sustained VT with an average of 8.8 per day. Additionally, the patient suffered from impaired physical performance due to decreased chronotropic competence. In July 2009, flecainide was added to the beta-blocker/verapamil regimen, resulting in a plasma level of 0.20 mg/L. No ICD shock or sustained VT occurred until December 2010. Genetic testing revealed an RyR2 receptor mutation. The case demonstrates the challenge of diagnosis and management of CPVT. It furthermore supports recent experimental evidence that the class I antiarrhythmic drug flecainide can suppress CPVT. The presented case supports a novel strategy in treating CPVT with the class I antiarrhythmic agent flecainide.

Introduction
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac arrhythmic disorder that can cause sudden cardiac death (SCD) due to ventricular fibrillation (VF). Catecholaminergic polymorphic ventricular tachycardia has been characterized in children but may also manifest during adulthood. Characteristically, CPVT-associated arrhythmic events are triggered by catecholaminergic stimulation. Thus, they occur under conditions of physical and also mental stress. Sudden noises, physical pain, fear, or sudden movements are all associated with catecholaminergic release, and these events can trigger arrhythmia in the setting of CPVT. Catecholaminergic polymorphic ventricular tachycardia can manifest as polymorphic ventricular extrasystoles (VES), bidirectional or polymorphic ventricular tachycardia (VT), or VF. Correspondingly, clinical symptoms range from mere palpitations to syncpe and SCD.

As for several other arrhythmic disorders, the cellular substrate for CPVT are afterdepolarizations. Patients suffering from CPVT have been identified to carry mutations of either the cardiac ryanodine receptor (RYR2; CPVT-1) or calsequestrin (CASQ2; CPVT-2). Both these mutations cause delayed afterdepolarizations by causing sarcoplastic reticulum (SR) Ca2+ overload and subsequent spontaneous Ca2+ release. Implantation of an automated cardioverter–defibrillator (ICD) has been considered as first-line therapy in patients with CPVT and documented VF; however, recently, evidence has been provided that this strategy has certain disadvantages. Thus, in comparison with other proarrhythmic diseases requiring ICD therapy, even modest exercise can initiate fast VTs triggering ICD shocks, which in turn can induce sustained VT or VF. In addition, ICDs do not seem to protect all patients. Thus, the prevention of VT is crucial even in ICD recipients for preventing impairment of quality of life due to repeated and potentially traumatizing shock delivery. To date, beta-blockers and Ca2+ antagonists of the verapamil type have been the antiarrhythmic pharmacotherapy of choice in the setting of CPVT. However, these agents completely suppress CPVT-associated VT in only a fraction of patients. Only recently a report has demonstrated the efficiency of the class I antiarrhythmic drug flecainide in suppressing ventricular tachyarrhythmia in a murine model of CPVT as well as in two human subjects suffering from CPVT.

Case
We here present the case of an otherwise healthy boy born in 1998 and suffering from CPVT. A timeline on the clinical events and the diagnostic and therapeutic measures of the case is given in Table 1. The child had suffered from recurrent syncpe since age 3. Although usually episodes occurred one to two times per year, an accumulation occurred in 2006 (six episodes) and during January 2007 (two episodes). Typically, the episodes appeared to be triggered by sudden stressful events such as noises, physical pain, physical movement, or fear. The patient’s mother reported that some of the episodes were preceded by a sudden headache. The episodes consisted of unconsciousness usually lasting for seconds. On recovery the boy was described as pale and appeared stunned. A minority of the episodes were described to be associated with stiffness of the arms and urination. The patient was admitted to the Department of Neuropediatrics at our institution. Physical and neurological examinations were normal. EEG testing did not
Table I  Time line of clinical events and diagnostic and therapeutic procedures

<table>
<thead>
<tr>
<th>Date</th>
<th>Event/procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 1998</td>
<td>Birth of the patient</td>
</tr>
<tr>
<td>Approx. since 2001</td>
<td>Recurrent syncopes (~1–2/year)</td>
</tr>
<tr>
<td>Since 2006</td>
<td>Accumulation of syncopes</td>
</tr>
<tr>
<td>2006/2007</td>
<td>Neurological evaluation: negative</td>
</tr>
<tr>
<td></td>
<td>Tilt table and Schellong test: negative</td>
</tr>
<tr>
<td></td>
<td>24 h Holter monitoring: multiple polymorphic VES</td>
</tr>
<tr>
<td></td>
<td>Exercise testing: stress-induced increase of VES</td>
</tr>
<tr>
<td></td>
<td>Echocardiography and MRI: normal</td>
</tr>
<tr>
<td></td>
<td>Electrophysiological testing: non monomorphic VT or supra-ventricular tachycardia</td>
</tr>
<tr>
<td>February 2007</td>
<td>Loop recorder implantation</td>
</tr>
<tr>
<td></td>
<td>Initiation of verapamil therapy</td>
</tr>
<tr>
<td>May 2007</td>
<td>Ventricular fibrillation and cardiopulmonary resuscitation</td>
</tr>
<tr>
<td></td>
<td>ICD implantation</td>
</tr>
<tr>
<td></td>
<td>Addition of beta-blocker therapy</td>
</tr>
<tr>
<td>November – February 2008</td>
<td>Recurrent ICD shocks</td>
</tr>
<tr>
<td></td>
<td>Dose escalation of verapamil and beta-blocker medication, resulting in clinically relevant bradycardia</td>
</tr>
<tr>
<td>June 2010</td>
<td>Initiation of flecainide therapy</td>
</tr>
<tr>
<td></td>
<td>Dose de-escalation of beta-blocker and verapamil medication</td>
</tr>
<tr>
<td>Since July 2009</td>
<td>No further ICD shocks, no further clinically relevant bradycardia</td>
</tr>
</tbody>
</table>

For dosages of the respective agents, we refer to the full text.
VES, ventricular extrasystoles; VT, ventricular tachycardia; ICD, implantable cardioverter–defibrillator.

In addition, the medical history of our patient demonstrates the adverse effects that chronic medication with beta-blockers and Ca²⁺ antagonists do not reliably suppress CPVT.1,3 Exercise testing revealed polymorphic ventricular extrasystoles under physical stress (Figure 2).

Cardiac imaging studies revealed no evidence for a structural heart disease: echocardiography was normal and left and right heart catheterization demonstrated normal haemodynamics with a normal right and left ventricle. Cardiac MRI with gadolinium application did not reveal any abnormality. During electrophysiological testing, polymorphic VES but no sustained VT or supraventricular tachycardia occurred. During orciprenaline administration, spontaneous polymorphic VES occurred that were similar to those observed during stress testing (Figure 2).

As it remained unclear whether the recurrent syncope was related to the stress-induced tachycardia, a loop recorder was first implanted (February 2007). Since even low doses (12.5 mg/day) of atenolol caused significant bradycardia, pharmacological therapy was switched to verapamil. A permanent dose of 90 mg verapamil/day was well tolerated and the patient was dismissed under this regimen.

No further syncope had occurred and no tachycardia was evident when a routine loop recorder control was conducted on 27 April 2007. On 19 May 2007 the boy was woken up by his mother after he had fallen asleep during a car ride. He collapsed and was immediately resuscitated by his mother and shortly thereafter by emergency medical personnel. Cardiopulmonary resuscitation was conducted and sinus rhythm was restored by defibrillation. Subsequent loop recorder analysis revealed a polymorphic VT with degeneration into VF (Figure 3). Thereafter, an ICD system was implanted. Additional drug therapy with bisoprolol was begun. After stepwise increase, a permanent dose of 7.5 mg/day (0.35 mg/kg body weight) was well tolerated. Neurological and physical recovery of the boy was complete and he was dismissed from the hospital.

Under this regimen, the patient was free of relapse until ICD shock delivery occurred in November 2007 and twice again on 11 February 2008. Implantable cardioverter–defibrillator interrogation revealed fast VT or VF corresponding to the relevant episodes. Subsequently, verapamil was again added to the beta-blocker medication (now bisoprolol 5 mg and verapamil 90 mg/day). After further shock delivery due to sustained VF under this regimen in July 2008, antiarrhythmic medication was escalated to 110 mg verapamil + 5 mg bisoprolol/day and then after further shock delivery in May 2009 to 120 mg verapamil + 5 mg bisoprolol/day.

Under a combination of bisoprolol and verapamil, the patient complained about reduced physical performance. Significant bradycardia was observed, resulting in antibradycardic pacemaker stimulation at 40 bpm during daytime hours. Baseline frequency was increased to 60 bpm, resulting in a high percentage of time stimulated.

On 2 July, flecainide was added to the antiarrhythmic medication consisting of the beta-blocker and the Ca²⁺ antagonist. Titration of flecainide to a permanent dose of 90 mg/day was well tolerated. Chronic administration of this dosage resulted in a plasma level of 0.20 mg/L. Simultaneously, verapamil was reduced to 60 mg/day. Routine ICD interrogations in September and November 2009 revealed a reduction of non-sustained VTs by almost a factor of 7 from 8.8 to 1.3 episodes/day. No VF, syncope, or shock delivery occurred until December 2010. Genetic analysis revealed no CASQ2 gene mutation; a cascade screening approach of the RYR2 gene led to the identification of a published missense mutation (c. 14311 G > A, p. V4771I) in heterozygous state as the cause for CPVT.

Discussion and review of the current literature

Only ICD implantation can reliably prevent SCD, therefore, it is generally agreed upon that in the setting of CPVT and documented VF or haemodynamically unstable VT, ICD implantation is the first-line therapy. However, our case emphasizes the need for additional pharmacological therapy to avoid repeated ICD shock delivery. These events can have a traumatizing impact and can severely limit the patient’s everyday activities and quality of life—may it be by repeated de facto shock delivery or the fearful expectation of these.

The case presented here adds to the clinical experience that beta-blockers and Ca²⁺ antagonists do not reliably suppress CPVT.1,3

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verapamil may have on physical performance by reducing chronotropic competence, thus—at least in our case—further severely reducing quality of life.

The recent report by Watanabe et al. is the first to consider a class I antiarrhythmic for the treatment of CPVT. The authors demonstrate a suppression of VT/VEs in a transgenic murine model of CPVT and two patients suffering from CPVT by administration
of flecainide. An additional case report on this topic has recently been published on a patient suffering from CPVT in which beta-blocker therapy was effective. Yet, other than in our case—where beta-blocker therapy was ineffective—beta-blocker therapy had to be terminated due to severe side effects and flecainide therapy was initiated as a substitute, which proved to be equally successful as beta-blocker therapy. The molecular mechanisms of CPVT-induced arrhythmia are comparatively well understood: mutations of either the cardiac ryanodine receptor—as has been confirmed in our case—or calsequestrin facilitate spontaneous Ca\(^{2+}\) release events from the SR. The sudden increase in cytosolic Ca\(^{2+}\) activates the Na\(^{+}/Ca^{2+}\) exchanger, resulting in an electrical inward current that may depolarize the cellular membrane to a potential from where a new—premature—action potential is triggered. Flecainide would act on two levels of this mechanistic cascade (i) by reducing RyR open probability, thus reducing spontaneous SR Ca\(^{2+}\) release, and (ii) by inhibition of Na\(^{+}\) current. Thus, the antiarrhythmic actions of flecainide in the setting of CPVT associated with either RYR2- or CASQ2-mutations are plausible. Results from several groups (C. Pott et al., submitted) have provided evidence that the cardiac Na\(^{+}/Ca^{2+}\) exchanger could function as a direct mediator of afterdepolarizations—most likely since the level of Ca\(^{2+}\)-induced membrane current is a direct function of the expression and activity level of the Na\(^{+}/Ca^{2+}\) exchanger. Since this would also hold true for CPVT-associated arrhythmia, an alternative future therapy in CPVT may be the pharmacological inhibition of the Na\(^{+}/Ca^{2+}\) exchanger, although the agents in question have so far only been tested in animal models.

In comparison, flecainide offers the unique advantage of being an approved drug that has been in use since 1972 and has few adverse effects in everyday use. The CAST trial has shown that class I antiarrhythmics are associated with an increased rate of SCD in post-infarct patients; however, CPVT typically is not associated with structural heart disease. Nevertheless, one should follow the usual precautions such as closely monitoring QRS width when administering class I antiarrhythmics in CPVT patients, and flecainide therapy should be combined with beta-blocker therapy.

As a matter of course, the data currently available are not substantial enough to uncritically advocate flecainide as the first-line medical therapy in CPVT patients implanted with an ICD. A larger patient population has to be investigated, including long-term follow-up. Nevertheless, flecainide treatment may be a promising strategy to increase the quality of life in patients suffering from CPVT. First, it may reduce or even totally suppress ICD shock delivery. Secondly, the adverse effects of high-dose beta-blocker or verapamil therapy could be avoided.

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References

Right atrial perforation at the end of an atrial fibrillation ablation procedure

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A 74-year-old man with chronic atrial fibrillation underwent ablation under conscious sedation. After sheath removal from the left atrium, the patient flexed his thighs, resulting in a ‘foetal position’ developing tamponade due to an right atrial (RA) appendage perforation from sheath migration. This illustrates the importance of close monitoring during sedation weaning, recommending removal of all sheaths prior to sedation withdrawal.

Introduction
Atrial fibrillation (AF) ablation is an invasive procedure associated with complications. In a large ‘real-world’ survey by Cappato et al.1 from 8745 patients, the incidence of major complications was 6%, including four deaths (two major cerebral thromboembolisms, one extrapercardial perforation, and an unknown cause). Major complications include death, stroke, cardiac perforation with tamponade, pulmonary vein stenosis >50%, and atrial–oesophageal fistula. The incidence of cardiac tamponade reported ranges from 0.6 to 1.2%1,2 depending on the series.

Case
A 74-year-old man with pectus excavatum and symptomatic AF was referred for ablation. He underwent uneventful AF ablation under conscious sedation; however, towards the end of the procedure and once both sheaths were pulled in the RA and inferior vena cava, the patient moved despite his restraints. He flexed his legs and thighs, achieving a nearly foetal position. Over the next few minutes he became hypotensive. Since the patient was fully anticoagulated with heparin (ACT 300–350 s), he received protamine and fresh frozen plasma. An echocardiogram confirmed the diagnosis of pericardial effusion with tamponade. He underwent echocardiogram and fluoroscopy-guided standard subxyphoid pericardiocentesis, but due to his pectus excavatum the procedure was difficult (Figure 1). Pericardiocentesis was performed with a 15 cm needle and an 8.3F drain. Intrapercardial position of the drainage was confirmed with agitated saline contrast injection. Due to the tamponade he became pulseless, requiring chest compressions resulting in dislodgement of the pericardial drain. The patient was then transferred to the operating room where he underwent repair of a 6 mm perforation of the RA appendage. He was discharged a few days later without neurologic sequelae.

Discussion
To the best of our knowledge, this is the first report of a right atrial appendage perforation following an AF ablation. We believe that migration of one of the transseptal sheaths was the culprit since all other catheters were already removed. This was supported by continuous intraprocedural real-time imaging with intracardiac echo, which did not reveal any pericardial effusion.

In this case, a patient recovering from sedation could have moved involuntarily with enough strength to release his restraints. Conscious sedation has been described by several experienced groups as safe for AF ablation.3 Furthermore, by allowing/keeping

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