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CASE REPORT

Treatment of Catecholaminergic Polymorphic Ventricular Tachycardia: *Lessons From One Case*

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List of Abbreviations
CASQ2 = calsequestrin-2 (cardiac form)
CPVT = catecholaminergic polymorphic ventricular tachycardia
ICD = implantable cardioverter-defibrillator
ECG = electrocardiogram
RyR2 = (cardiac) ryanodine receptor 2
VF = ventricular fibrillation
VT = ventricular tachycardia

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ABSTRACT

We report a case of a 27-year-old female with catecholaminergic polymorphic ventricular tachycardia, presenting with syncope during emotional stress. Treatment with a β-blocker alone was ineffective, whereas the addition of amiodarone prevented arrhythmia-relapses for 28 months. In view of planned pregnancy, amiodarone was substituted with flecainide, coupled with defibrillator-implantation. Fourteen months later, the patient had 3 appropriate, followed by 3 inappropriate shocks. This case highlights the short-comings of pharmacological treatment and the limitations of device-therapy; the high rate of inefficacious shocks, along with the proarrhythmic potential, point towards the judicious use of defibrillators, aiming at shock-delivery only for ventricular fibrillation.

INTRODUCTION

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a primary electrical disease characterized by normal resting electrocardiogram (ECG) and ventricular arrhythmias induced by adrenergic stress, in the absence of structural heart disease.[1] CPVT is caused by mutations in the cardiac ryanodine receptor 2 (RyR2) or in the sarcoplasmic reticulum protein calsequestrin-2 (CASQ2),[1] which cause enhanced calcium release (from the sarcoplasmic reticulum) and abnormal intracellular calcium overload; these changes result in polymorphic ventricular tachycardia via triggered activity. CPVT presents invariably with syncope in children or young adults and can lead to sudden cardiac death.[1] In patients unresponsive to pharmacological treatment, implantable cardioverter-defibrillators (ICDs) have been advocated,[2,3] but the efficacy and safety of this therapy remain uncertain.

We describe a case of a young female patient with CPVT and an implanted ICD, who had 3 appropriate, followed by 3 inappropriate shocks during a single episode; after the third inappropriate shock, a couplet of premature ventricular beats was observed, followed by gradual decrease of sinus rate below the (re)detection interval. If sustained polymorphic ventricular tachycardia had re-occurred after the sixth shock, the outcome might have been fatal, as the device had exhausted its therapies for a single episode. This case illustrates the short-comings of pharmacological treatment

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in CPVT, and also the high rate of inefficacious shocks and the proarrhythmic potential of ICD-therapy.

CASE PRESENTATION

A 27-year old female presented with multiple episodes of palpitations and dizziness, as well as with two syncopal events, all during intense emotional distress. She denied family history of sudden cardiac death. Physical examination, resting 12-lead ECG and echocardiography were unremarkable, but a 24-hour Holter recording showed sustained polymorphic ventricular tachycardia (VT) (Figure 1A).

DIAGNOSTIC EVALUATION

On admission to the University Hospital, serum electrolytes, troponin I and thyroid function tests were all within normal limits. Serial 12-lead ECGs and echocardiographic evaluations were normal; coronary angiography revealed normal coronary arteries and cardiac magnetic resonance imaging was unremarkable. Based on these results, polymorphic VT associated with an acute coronary syndrome or myocarditis was excluded, as was structural heart disease, such as hypertrophic and dilated cardiomyopathies or arrhythmogenic right ventricular dysplasia.

The patient underwent maximal exercise tolerance testing, without signs of myocardial ischemia or ventricular arrhythmias. Baseline QT was normal, which shortened during exercise; these findings argued against short QT or long QT syndromes. Atrial fibrillation in the presence of an accessory pathway was ruled out after injection of 12 mg of adenosine, which induced transient complete atrio-ventricular block. Similarly, Brugada syndrome was ruled out based on the absence of electrocardiographic changes after procainamide testing at 10 mg/kg.

An electrophysiological study showed normal conduction intervals, sinus node recovery time, atrio-ventricular nodal effective refractory period, retrograde atrial activation sequence and ventricular effective refractory period. After isoproterenol infusion, QT shortening was noted, thereby excluding long QT1.[4] However, non-sustained polymorphic VT appeared spontaneously after isoproterenol administration; as no R-on-T phenomenon was seen, the short-coupled variant of torsade de pointes was considered unlikely.[5] In some runs of non-sustained polymorphic VT, characteristics of bidirectional tachycardia were noted (Figure 1B). These findings were considered diagnostic of CPVT, despite subsequent negative genotype testing results, which included mutation screening for RyR2 or CASQ2.

TREATMENT

Treatment with β-blockade (250 mg of metoprolol tartrate daily, in three divided dosages of 100 mg, 50 mg and 100 mg) was commenced, followed by symptomatic improvement, although runs of polymorphic VT were recorded on 24-Holter

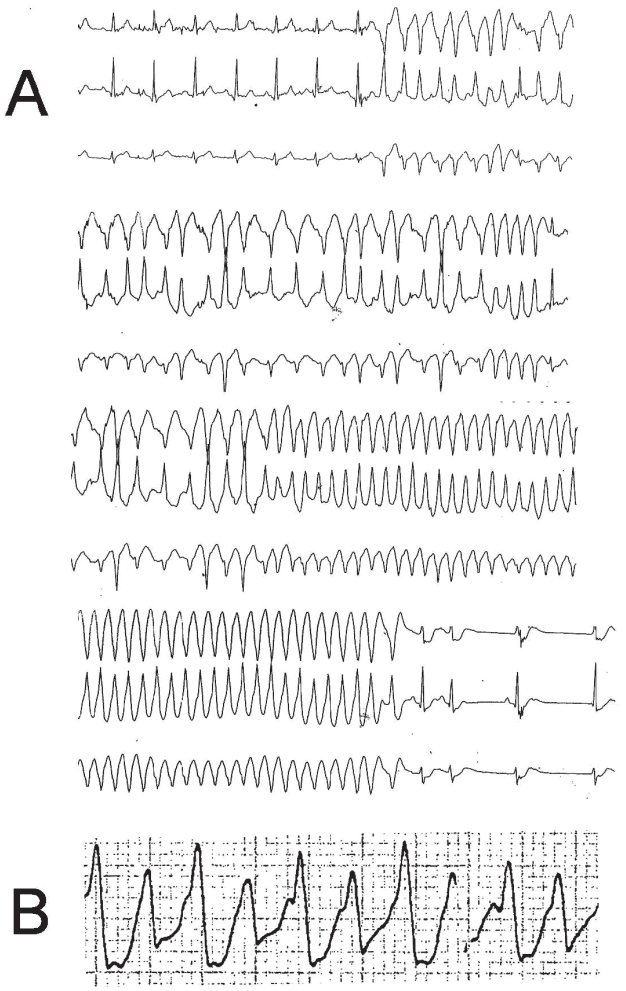

FIGURE 1. Polymorphic ventricular tachycardia. Panel A: spontaneous polymorphic ventricular tachycardia during emotional stress. Panel B: ECG strip showing bidirectional ventricular tachycardia after isoproterenol infusion.

during follow-up. However, 4 months after the initial submission, the patient was re-admitted for palpitations and syncope; echocardiography was again normal. Intravenous amiodarone was commenced, followed by oral maintenance dose at 200 mg daily. Due to concerns regarding ICD therapy in CPVT,[6,7] ICD implantation was deferred and pharmacologic antiarrhythmic treatment was chosen. Despite the limited experience with amiodarone in CPVT, oral treatment was continued, with absence of VT recurrence for 28 months. At this point, the patient reported that she was contemplating pregnancy (for which no hormonal therapy was prescribed); in view of the possibility of fetal toxicity,[8] amiodarone was discontinued. Metoprolol was continued, but amiodarone was substituted with flecainide 100 mg bid, based on the favorable safety profile of this agent during pregnancy;[9] more importantly, this

treatment was selected based on early promising reports on the use of flecainide in patients with CPVT.[10] Because of the absence of ventricular arrhythmias during baseline exercise testing, repeat testing was not used as a means of evaluating the efficacy of pharmacological treatment.

Given the inability to ascertain the efficacy of pharmacological treatment by exercise testing and the relatively weak data on flecainide at that time, the option of defibrillator-therapy was proposed. The limitations of such therapy in CPVT[6,7] were explained to the patient, but she eventually underwent ICD implantation (Secura DR, *Medtronic, Inc.*, Minneapolis, Minnesota, USA) after obtaining a second opinion. No defibrillation testing was performed prior to discharge, and the fibrillation detection interval was programmed at 330 ms, with all shocks at maximum energy. A tachycardia monitor-only zone was programmed at 370 ms. Stability and onset criteria were programmed off, but PR-logic was programmed on for atrial flutter/fibrillation and sinus tachycardia; this algorithm aids in the discrimination of ventricular from supraventricular rhythms by monitoring the stability of the PR (or RP) intervals during tachycardia.

ICD DISCHARGES

Fourteen months after ICD implantation, the patient had a syncopal episode on exertion, while on treatment with flecainide and metoprolol; the patient recalled 3 ICD-shocks. Device interrogation (Figures 2 & 3) revealed an episode of polymorphic VT (Figure 2, panel a), which was not terminated by a 35-Joule biphasic shock. Episodes of atrial tachycardia were then recorded in the atrial channel (Figure 3), whereas the ventricular channel displayed 2 further (appropriate) unsuccessful shocks for polymorphic VT (Figure 2, panels b and c). Spontaneous termination of polymorphic VT occurred after the third shock (Figure 2, panel d), but sinus tachycardia (with frequent atrial premature depolarizations, Figure 3) caused 3 inappropriate shocks (Figure 2, panels e, f, g); these were caused by irregular ventricular intervals that fulfilled the redetection criteria. Of note, the device redetection algorithms consider a ventricular arrhythmia event terminated if 8 consecutive ventricular intervals longer than the programmed ventricular fibrillation (VF) detection interval are present after discharge, or when 20 seconds elapse during which the median of the last 12 ventricular intervals is longer than the

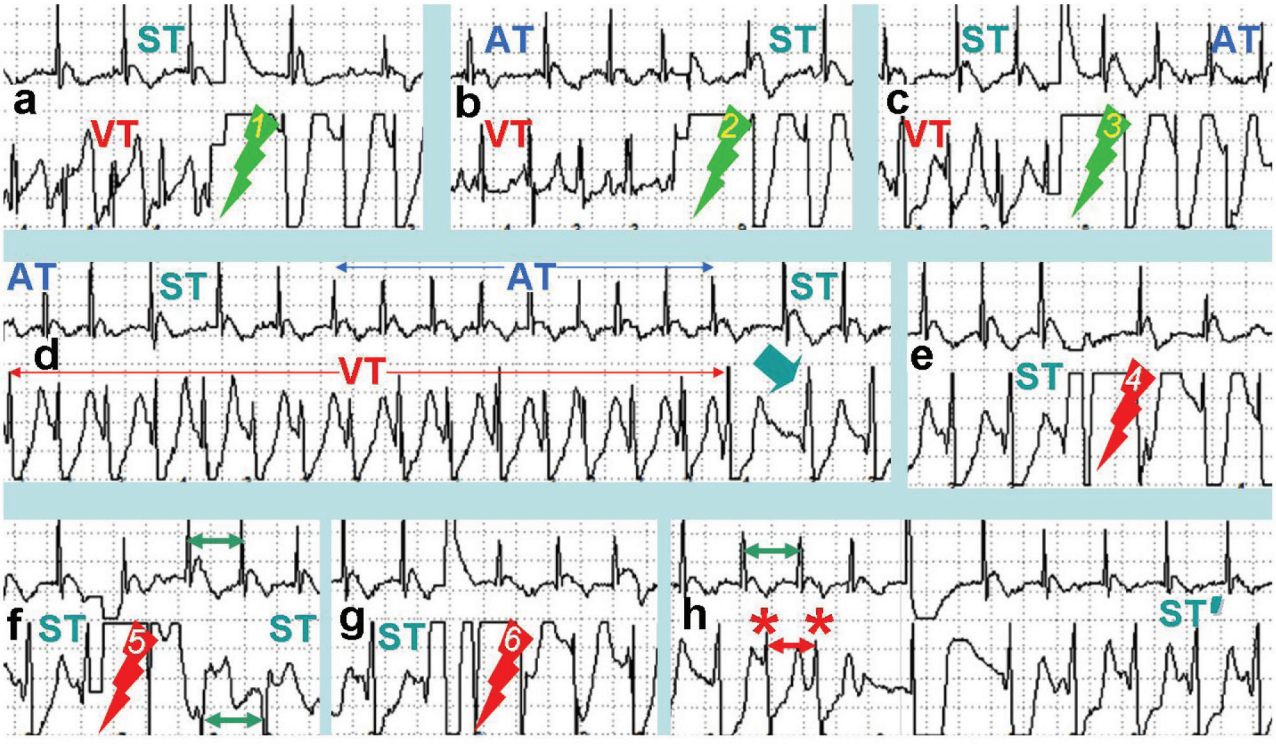

FIGURE 2. Device interrogation (1). Polymorphic VT (panels a, b, c), not terminated by three 35-Joule biphasic shocks. Episodes of non-sustained atrial tachycardia (AT) were observed after the 1st shock; VT terminated spontaneously after the 3rd shock (panel d), but sinus tachycardia (ST, arrow) caused 3 inappropriate shocks (panels e, f, g), followed by sinus rate lowering (ST′) and episode termination (panel h). Note the couplet of premature ventricular beats (asterisks, panel h), characterized by unequal atrial (green double arrow) and ventricular (red double arrow) coupling intervals. Had this arrhythmia proceeded into another episode of polymorphic VT, this would have been untreated, because the device had exhausted its therapeutic capacity for a single episode.

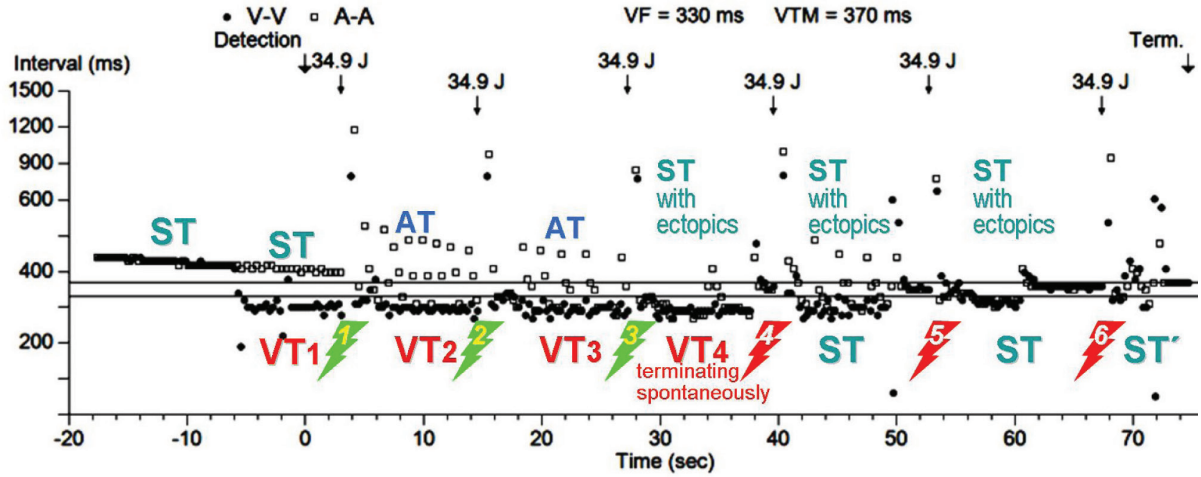

FIGURE 3. Device interrogation (2). Summary of the entire arrhythmic event marked with a time-scale. Note the four polymorphic ventricular tachycardia episodes (the last of which terminated spontaneously prior to shock delivery) and the ensuing sinus tachycardia with frequent atrial premature depolarizations, causing inappropriate shocks.

VF detection interval. After the sixth discharge, sinus heart rate lowered and the episode terminated (panel h). If another episode of polymorphic VT had occurred, this would have been untreated, because the device had exhausted its therapeutic capacity for a single episode.

To avoid therapies for polymorphic VT, the fibrillation detection interval was reprogrammed to 270 ms, aiming at the delivery of shocks only for ventricular fibrillation. In addition, a stability interval of 40 ms was programmed in the supraventricular discriminator-algorithms. After device reprogramming, no further shocks occurred during an 8-month follow-up period.

DISCUSSION

Our case of CPVT unfolds several features of interest in this rare disease. These are herein highlighted.

CLINICAL PRESENTATION AND DIAGNOSIS

In our patient, CPVT was diagnosed clinically, based on previous criteria,[1] which include adrenergically-mediated polymorphic or bidirectional tachycardia, in the absence of structural heart disease and normal ECG (absence of Brugada-like pattern and normal QT interval at rest, during exercise and after isoproterenol administration). The disease was nongenotyped, which is in line with previous observations in a cohort of 30 patients,[2] indicating that nongenotyped-CPVT is seen mostly in female patients with late presentation. In general, it is estimated that RyR2 or CASQ2 mutations are identified in only ~60% of patients presenting with a strong CPVT phenotype.[11]

A threshold heart rate (approximately 130 bpm) has been suggested,[12] above which exercise-induced VT invariably appears in these patients, but, in our case, the conditions eliciting VT varied. Specifically, no VT was noted during exercise test (with an attained peak heart rate of 189 bpm), whereas emotional stress associated with much lower sinus rates (~120 bpm) induced sustained polymorphic VT. This variability regarding threshold heart rate and precipitating conditions should be taken into account during clinical assessment; moreover, an important lesson from this case is that a negative exercise test does not exclude the diagnosis of CPVT. In this respect, a negative exercise test not only raises diagnostic difficulties, but also deprives a simple means of evaluating the pharmacological regimens during follow-up.

TREATMENT

β-Blockade remains the mainstay treatment in CPVT, but it may prove ineffective in ~30% of cases.[1,2] Amiodarone exerts potent antiarrhythmic actions via all known pharmacologic mechanisms, but there is no published experience with the use of this agent in CPVT. In our patient, oral amiodarone (at 200 mg daily) was associated with absence of arrhythmia recurrence during a 28-month follow-up period. Thus, amiodarone added to β-blockade appears effective in CPVT resistant to monotherapy, although more data are needed; nonetheless, the non-cardiac side-effect profile of amiodarone should be taken into account, especially in young patients, including females in child-bearing age.

Flecainide decreases spontaneous calcium-release from the sarcoplasmic reticulum by cardiac ryanodine receptor inhibition, but also suppresses triggered beats by sodium-channel blockade.[10] The efficacy of this agent has been confirmed in 33 patients with genotype-positive[13] and in 12 patients with

genotype-negative CPVT.[14] Arrhythmia relapses occurred in 1 patient (3%) over (a median of) 20 months in the first series[13] and in 2 patients (16%) over (a mean of) 48 months in the second series,[14] possibly due to noncompliance in all three. In our patient, flecainide (200 mg daily) suppressed ventricular arrhythmias initially, but VT relapse occurred 14 months after treatment initiation, despite adequate compliance to the drug regimen.

DEVICE THERAPY

ICD implantation has been suggested in patients unresponsive to medical treatment.[2] In a report of 20 pediatric patients with symptomatic CPVT,[3] failure of high-dose β-blockade was recorded in 13 patients; of these, 8 refused ICDs, and eventually 6 (75%) died suddenly. However, the pattern of electrical storm not terminated by recurrent ICD shocks described in our patient was observed in 4 of the 5 patients who received ICDs in this cohort;[3] as in our patient, these VT-storms terminated spontaneously after delivery of the programmed ICD shocks, without degeneration to ventricular fibrillation. By contrast, fatal outcome of electrical storm has been reported in 2 other patients with CPVT and implanted defibrillators.[6,7] The mechanism is thought to be catecholamine release, mediated by shocks, triggering a vicious cycle of VT and device discharges.

In our patient, the examination of stored electrograms by the device and the overview of the detection intervals add more information on device (and pharmacological) therapy in CPVT. Specifically, four points should be noted.

(*a*) As in a recently reported case of a 22-year-old patient with CPVT,[15] our patient had 3 unsuccessful shocks for polymorphic VT. Whether this represents high defibrillation threshold in these patients or whether the arrhythmia reinitiates immediately after the shock cannot be accurately determined and requires further investigation. Defibrillation testing post-implantation may be useful in this regard.

(*b*) High sinus rate was observed after VT termination, despite β-blockade at high dosages, interfering with the arrhythmia-detection process by the device, and similar findings were reported previously in a patient receiving 300 mg of atenolol.[7] Thus, 'ultra-high' dosages of β-blockers have been recommended in CPVT patients, with the possible addition of verapamil.[7] In cases of positive baseline exercise testing, repeat testing should be used during follow-up to ascertain adequate response to pharmacologic treatment.[7]

(*c*) A subset of CPVT-patients have also catecholamine-induced atrial arrhythmias,[16] which cause further interference with VT detection by the device.[7] Although repeated 24-hour Holter recordings failed to reveal atrial arrhythmias in our patient, episodes of non-sustained atrial tachycardia were observed after the first shock; thus, the prevention of atrial arrhythmias and lowering the ventricular response are additional therapeutic targets in CPVT patients, even in the absence of clinical manifestations.

(*d*) A different ICD-programming strategy should be employed in CPVT, compared to other indications; due to frequent VT recurrences after ICD shocks, ICD therapy in CPVT should be targeted at prompt defibrillation, in cases of degeneration of polymorphic VT to ventricular fibrillation. This implies programming the fibrillation detection interval to sufficiently low values, thereby preventing not only inappropriate shocks, but also device-therapies for polymorphic VT.

LEFT CARDIAC SYMPATHETIC DENERVATION

Pharmacological antiarrhythmic therapy is of paramount importance in CPVT, but in drug-resistant cases sympathetic denervation should be contemplated; this treatment can be performed without significant complications and has been shown to reduce arrhythmia recurrences.[17]

CONCLUSION

Our case illustrates the short-comings of pharmacological treatment in CPVT during long-term follow-up, but also emphasizes the limitations of ICD therapy; the high rate of inefficacious shocks, along with the proarrhythmic potential, point towards the judicious use of this therapy. In implanted devices, meticulous programming is required to prevent inappropriate shocks. Left cardiac sympathetic denervation may be a viable therapeutic alternative in such cases.

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