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ADVANCED

CASE REPORT: CLINICAL CASE

Cardiac Transplantation for Refractory Catecholaminergic Polymorphic Ventricular Tachycardia

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ABSTRACT

We present a patient with catecholaminergic polymorphic ventricular tachycardia who failed maximal antiarrhythmic drug therapy and bilateral sympathetic denervation, who presented with syncope and recurrent ventricular tachycardia for 11 min refractory to 21 shocks. She underwent cardiac transplantation as curative treatment for refractory ventricular arrhythmias in catecholaminergic polymorphic ventricular tachycardia. (**Level of Difficulty: Advanced.**)

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A 27-year-old woman with catecholaminergic polymorphic ventricular tachycardia (CPVT) presented in 2019 following syncope. She described sudden-onset dizziness while walking and then received several implantable cardioverter defibrillator (ICD) shocks resulting in loss of consciousness. She awoke denying chest pain, shortness of breath, palpitations, weakness, or incontinence before the event. On hospital arrival, she noted only chest soreness. She denied recent illness, decreased oral intake, stress, or recent changes in medication, which included propranolol LA 60 mg daily, verapamil 120 mg daily, and flecainide 150 mg twice daily.

LEARNING OBJECTIVES

- Review initial CPVT medical management.
- Discuss advanced medical therapy and surgical options for management of CPVT.
- Suggest consideration of cardiac transplantation as a final approach for severe, refractory cases of CPVT.

Vital signs were blood pressure 111/68 mm Hg, heart rate 60 beats/min, and respiratory rate of 16 breaths/min saturating 98% on room air. Her physical examination was unremarkable, including regular cardiac rate and rhythm, no cardiac murmur, clear lungs bilaterally, soft abdomen, and no significant lower extremity edema. Laboratory data showed potassium 3.0 mmol/l, magnesium 1.8 mmol/l, troponin 12.34 ng/ml, creatine kinase 1,192 U/l, brain natriuretic peptide 15 pg/ml, thyroid stimulating hormone 0.97 μIU/ml, and flecainide level of 0.43 μg/ml.

Propranolol LA was increased to 120 mg daily and her electrolytes were repleted. Transthoracic echocardiogram showed preserved left ventricular ejection fraction with no regional wall motion abnormalities. ICD interrogation revealed persistent

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ABBREVIATIONS AND ACRONYMS

COR = class of recommendation

CPVT = catecholaminergic polymorphic ventricular tachycardia

ICD = implantable cardioverter defibrillator

VF = ventricular fibrillation

VT = ventricular tachycardia

ventricular tachycardia (VT)/ventricular fibrillation (VF) refractory to multiple ICD shocks over 11 min. Given persistent, refractory ventricular arrhythmias in a patient with CPVT as described as follows, cardiac transplantation evaluation was initiated.

PAST MEDICAL HISTORY

The patient was diagnosed with ryanodine receptor mutation CPVT at the Gly2295 amino acid as a child after her mother died from the condition at 22. For years, the patient was asymptomatic, ultimately requiring medical management following episodic VT. The arrhythmia was well controlled for several subsequent years before she suffered a syncopal episode leading to placement of a St. Jude Medical dual-coil Ellipse DR 2411-36C ICD device in 2010.

Three years before the index admission, the patient's course worsened, with several episodes of recurrent VT. Despite compliance with ultimately 3 drugs (nadolol, verapamil, and flecainide), she experienced recurrent syncope. After bilateral thoracoscopic sympathectomy in 2018, the patient reported significant improvement in palpitations, and she did very well clinically overall. Device interrogations in the interim showed rare atrial arrhythmias and no therapies delivered due to recurrence of VT on her medication regimen of propranolol, verapamil, and flecainide. Attempts at down titration of verapamil and propranolol were unsuccessful because of profound increase in palpitations.

DIFFERENTIAL DIAGNOSIS

Given known history of CPVT, the differential diagnosis for this presentation started with refractory CPVT due to exercise or subtherapeutic medication levels. Other potential explanations included medication or drug toxicity or noncompliance, hyperthyroidism, and electrolyte abnormalities. The multidisciplinary team felt that given the refractory nature of this patient's CPVT, this presentation was likely a breakthrough VT episode without exercise despite maximal medical therapy.

INVESTIGATIONS

Flecainide level was therapeutic. Urine drug screen was negative. Initial electrocardiogram showed an atrial-paced rhythm, otherwise unremarkable. Chest radiograph and computed tomography did not show any acute processes, noting a left-sided ICD generator with leads in the right atrial appendage and ventricular apex.

ICD interrogation showed the device functioning normally with appropriate settings (Table 1). Review of events revealed 11 recurrent episodes of VT or VF over 11.5 min, with the last episode persisting for nearly 4 min (Table 2). The ventricular arrhythmias were refractory to a total of 14 antitachycardia pacing (ATP) episodes and 21 ICD discharges. In the final event, VF persisted despite maximal ICD discharge capacity, with interrogation noting "No More Therapies" (Figure 1). VF continued for 53 s after the last ICD shock before spontaneously converting to normal sinus rhythm (Figure 2).

MANAGEMENT

The patient was continued on propranolol, verapamil, and flecainide during her admission. The patient experienced occasional, mild dizziness with ambulation but remained hemodynamically stable, and no arrhythmias were noted on telemetry. She was listed for cardiac transplantation as United Network for Organ Sharing Status 2.

After 10 days, cardiac transplantation was performed. Pre-operative transesophageal echocardiogram showed normal left ventricular ejection fraction, prominent left ventricular hypertrophy, and no significant valvular dysfunction. The surgery and post-operative course were uncomplicated.

TABLE 1 ICD Settings on Presentation

Device Test Results	Capture	Sense	Lead Impedance
A	1.0 V @ 0.5 ms	2.1 mV	380 Ω
V	1.625 V @ 1.0 ms	4.2 mV	310 Ω
HV			40 Ω
Device Parameters			
Mode	DDDR		
Base Rate	60 beats/min		
Max Track Rate	125 beats/min		
Zone Configuration	**VT-1**	**VT-2**	**VF**
Detection criteria	144 beats/min	181 beats/min	214 beats/min
Therapy (enabled)		ATP ×4 ATP ×4 800 V 875 V ×2	ATP ×1 800 V 875 V 875 V ×4

ATP = antitachycardia pacing; DDDR = dual-chamber, rate-modulated; ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

DISCUSSION

CPVT is a rare type of polymorphic VT that occurs in the absence of structural heart disease or associated syndromes. Most CPVT cases are associated with gene mutations in ryanodine receptor or calsequestrin 2, either of which increases calcium release from the cardiomyocyte sarcoplasmic reticulum during diastole, resulting in intracellular calcium overload and delayed after-depolarizations and triggered activity (1,2).

The clinical presentation of CPVT varies from asymptomatic (genetic diagnosis) to pre-syncope, syncope, or cardiac arrest secondary to VT or VF, often triggered by stress (3). Diagnostic testing for CPVT is challenging given the transient and sometimes fatal nature of the arrhythmia. If an episode of CPVT is captured on electrocardiogram, the typical finding is polymorphic VT with beat-to-beat QRS morphology variation or bidirectional tachycardia (4). CPVT is often identified through genetic testing, typically after a family member has been diagnosed. This patient fulfilled the Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society consensus statement covering diagnosis of CPVT (5).

Patients with CPVT should be instructed to limit stress and avoid strenuous sporting (Class I). Patients who are symptomatic (Class I), asymptomatic (Class IIa), or carriers of pathogenic mutations (Class IIa) should be started on nonselective beta-blocker therapy; nadolol is preferred (5,6). Even with beta-blocker therapy, an ICD may be required. The rate of breakthrough arrhythmias on beta-blocker therapy ranges from 3% to 11% annually (7). Therefore, patients should be assessed for recurrent ventricular arrhythmias even after initiation of beta-blocker therapy.

If ventricular arrhythmias recur despite beta-blocker therapy in patients with CPVT, a second medication, either an antiarrhythmic, such as flecainide, or a calcium channel blocker, such as verapamil, is added to the medication regimen (Class IIa), and ICD implantation is recommended (Class I) (5).

Patients with CPVT should continue escalation of medical management as indicated after ICD placement. If, despite medical therapy and ICD implantation, patients with CPVT continue to have recurrent ventricular arrhythmias, there should be consideration of a third medication or evaluation for cardiac sympathetic denervation (Class IIb) (5).

The effectiveness of ICD therapy for management of CPVT depends on the mechanism of arrhythmia.

TABLE 2 Summary of ICD Therapies Delivered During Refractory CPVT

Time	Type	Rate (beats/min)	Duration (M:S)	Therapy Delivered
3:02 PM	VF	214	1:01	ATP, 800 V, 875 V
3:03 PM	VT-2	196	0:59	ATP ×4, 800 V
3:04 PM	VT-2	193	0:30	ATP
3:05 PM	VF	214	0:42	ATP, 800 V
3:05 PM	VF	214	0:37	ATP, 800 V, 875 V
3:06 PM	VF	214	0:43	ATP, 800 V
3:07 PM	VF	214	0:21	ATP, 800 V
3:07 PM	VF	214	0:33	ATP, 800 V
3:08 PM	VF	214	1:25	ATP, 800 V, 875 V, 875 V ×2
3:09 PM	VF	214	0:40	ATP, 800 V, 875 V
3:10 PM	VF	214	3:54	ATP, 800 V, 875 V, 875 V ×4

CPVT = catecholaminergic polymorphic ventricular tachycardia; M:S = minutes:seconds; other abbreviations as in Table 1.

Appropriate ICD shocks delivered to polymorphic or bidirectional VT often fail, but shocks delivered to VF are usually effective (8,9). However, inappropriate shocks are common (8,10). Furthermore, serial defibrillation can perpetuate enhanced adrenergic stimulation and electrical storm (10), as likely occurred in this patient and made her refractory to recurrent ICD shocks.

FOLLOW-UP

The patient has had no further evidence of arrhythmia since cardiac transplantation.

CONCLUSIONS

CPVT is often well controlled through single- or dual-agent medical management, with ICD placement as indicated. Breakthrough episodes of VT/VF generally respond to up titration of baseline medications and, if necessary, addition of a third medication. Cases not amenable to multimodal medical management are typically referred for bilateral thoracoscopic cardiac sympathectomy. In this unusual refractory case, cardiac transplantation was the only remaining therapy. To our knowledge, this is the first case of cardiac transplantation as curative treatment for refractory CPVT.

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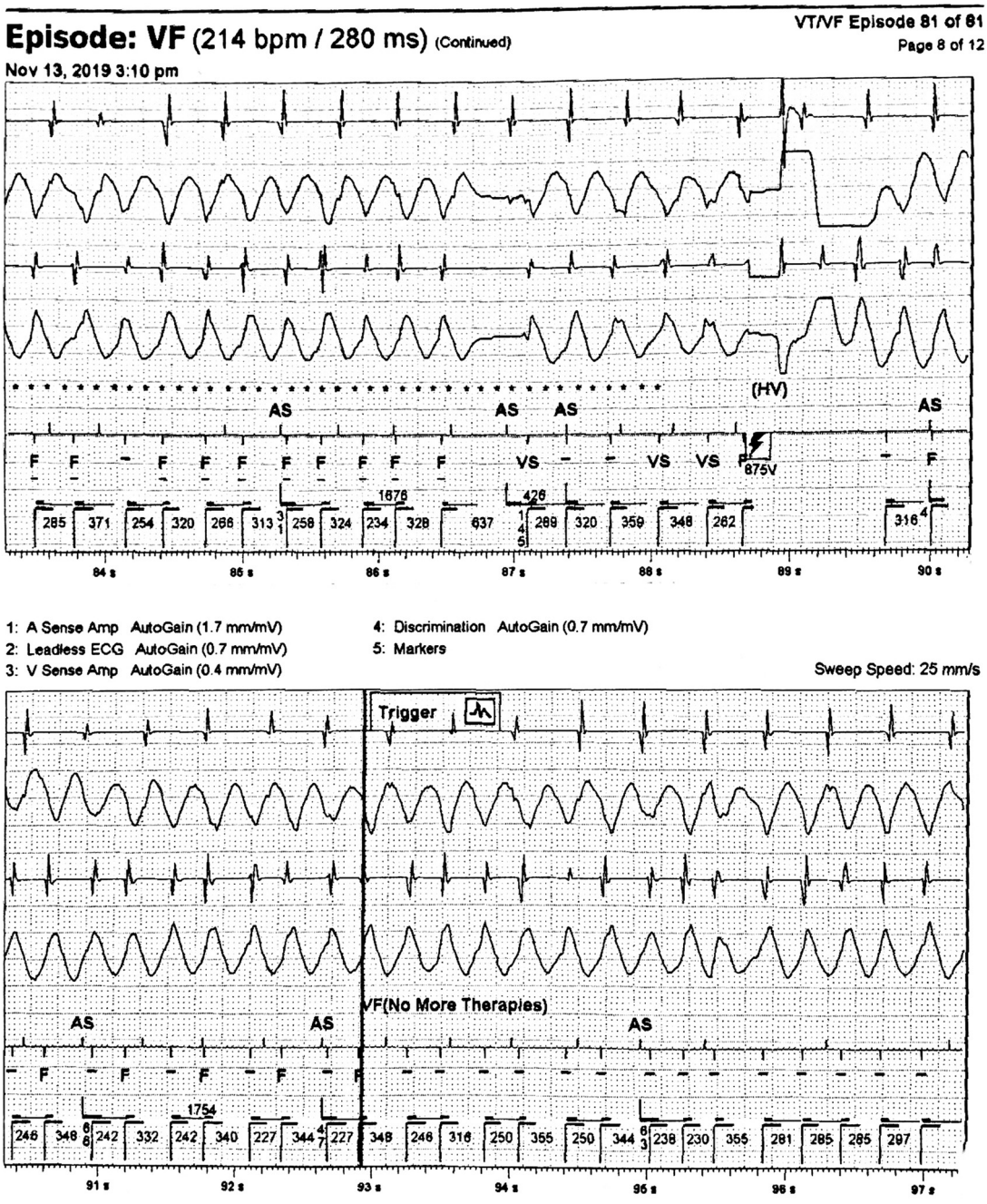
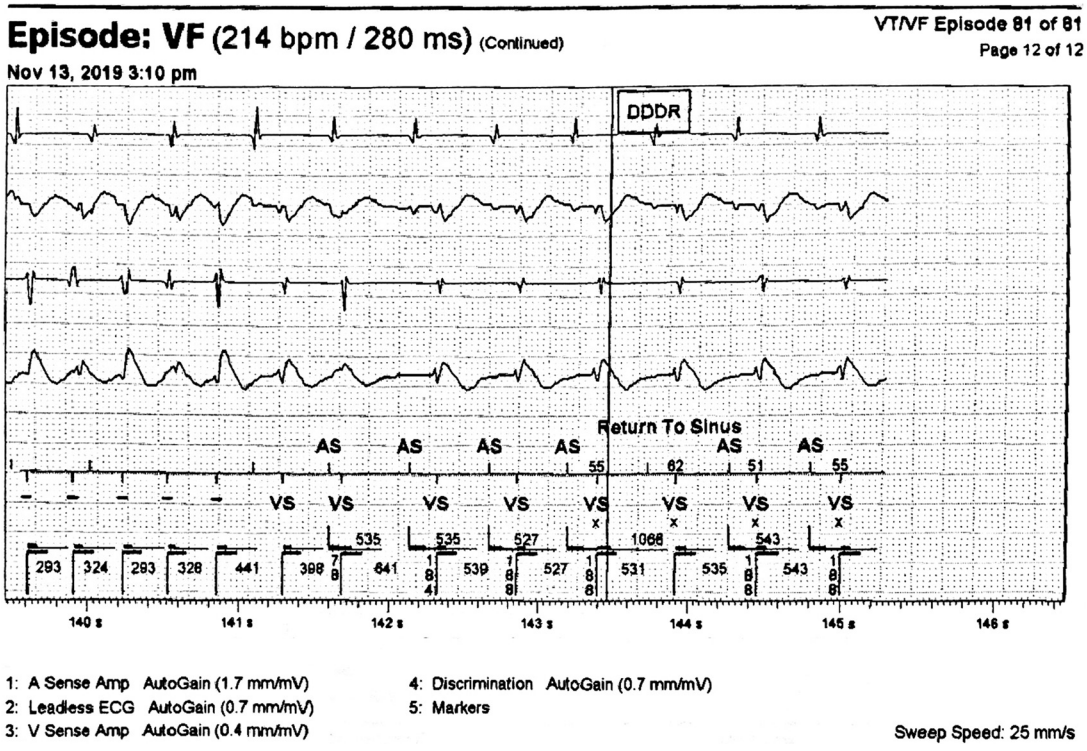
FIGURE 1 **Ventricular Fibrillation Refractory to Maximal ICD Discharges**



This figure shows the implantable cardioverter defibrillator (ICD) interrogation from this patient showing persistent ventricular tachycardia refractory to defibrillation. Ultimately, 93 s after onset of the patient's final episode of ventricular fibrillation (VF), the ICD exhausted all therapies. AS = atrial sensing; F = fibrillation; HV = high-voltage therapy; VS = ventricular sensing.

FIGURE 2 **Spontaneous Conversion of Refractory CPVT**



This figure shows that after approximately 142 s of refractory ventricular fibrillation, this final episode of arrhythmia spontaneously converted to normal sinus rhythm. AS = atrial sensing; CPVT = catecholaminergic polymorphic ventricular tachycardia; VS = ventricular sensing.

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