

# Exercise prescription using an insertable cardiac monitor in a patient with catecholaminergic polymorphic ventricular tachycardia



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## Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a lethal arrhythmic disease that can cause sudden cardiac death in young patients, with variants in the ryanodine receptor 2 (*RyR2*) as the primary causative gene.<sup>1</sup> Hence, an accurate diagnosis is essential for appropriate management. However, its diagnosis is usually delayed because of misdiagnosis as epilepsy.<sup>2–4</sup>

With respect to treating the disease, exercise restriction is vital in preventing the occurrence of lethal arrhythmia, and some medications, such as beta blockers and flecainide, are considered effective.<sup>5</sup> Conversely, it is still unclear whether an implantable cardiac defibrillator (ICD) improves the prognosis of CPVT.<sup>6,7</sup> In addition, some patients may refuse to undergo ICD implantation.<sup>7</sup> Herein, we present a case of CPVT in a 19-year-old woman who was implanted with an insertable cardiac monitor (ICM), which was effective in diagnosis and management, including exercise restriction.

## Case report

A 19-year-old woman had been suffering from syncope with exertion since the age of 5 years. Based on the abnormal findings of her electroencephalogram ([EEG] spike and wave complex generalized), she was diagnosed with epilepsy. Although she had been treated with 3 types of anticonvulsants, the syncope recurred; moreover, the frequency of

## KEY TEACHING POINTS

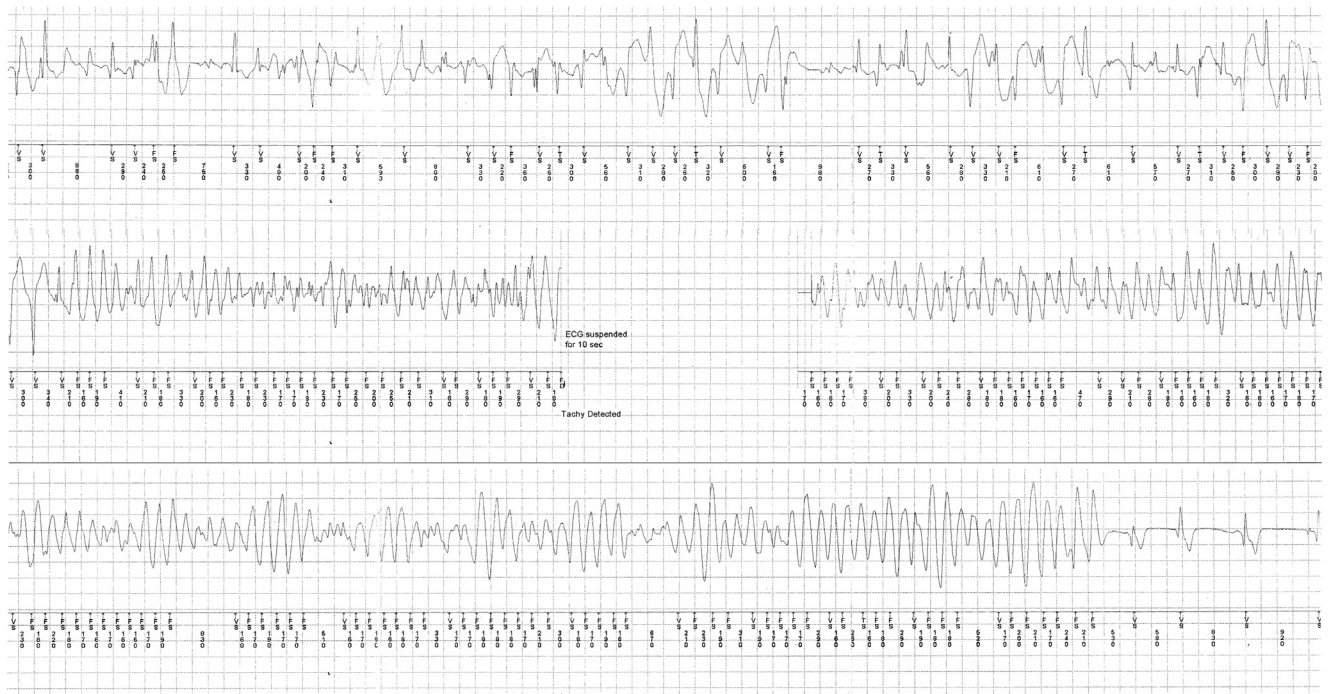
- Catecholaminergic polymorphic ventricular tachycardia (CPVT) is often misdiagnosed as epilepsy and early diagnosis is vital for its precise treatment.
- Recognizing the frequency of daily arrhythmia and supervision of compliance regarding exercise restriction is of paramount importance in the management of CPVT.
- An insertable cardiac monitor is highly useful as a diagnostic and a follow-up tool in patients with CPVT and it helps to make their daily lives easier.
- Genetic testing including the trio analysis is one of the effective ways to make an early and accurate diagnosis of CPVT, especially in cases where clinical diagnosis is difficult.

syncope-related events has worsened. She had no other significant past medical history. On physical examination, no abnormal findings were observed.

A 12-lead electrocardiogram (ECG) showed sinus bradycardia without a coved-type ST-segment elevation in the anterior precordial leads, J wave, and QT prolongation. Peripheral blood tests, echocardiography, cardiac computed tomography, and cardiac magnetic resonance imaging were all unremarkable. An exercise test reproducibly induced polymorphic premature ventricular contractions (PVCs) at 7 metabolic equivalents (METs) and nonsustained bidirectional and polymorphic ventricular tachycardia at 10 METs. A drug tolerance test also provoked a nonsustained bidirectional ventricular tachycardia after epinephrine injection. The arrhythmia

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**Figure 1** The electrocardiogram from an insertable cardiac monitor during syncope. Electrocardiography with an insertable cardiac monitor revealed bidirectional sustained ventricular tachycardia following ventricular fibrillation coupled with a syncopal attack while climbing stairs. The ventricular fibrillation resolved spontaneously.

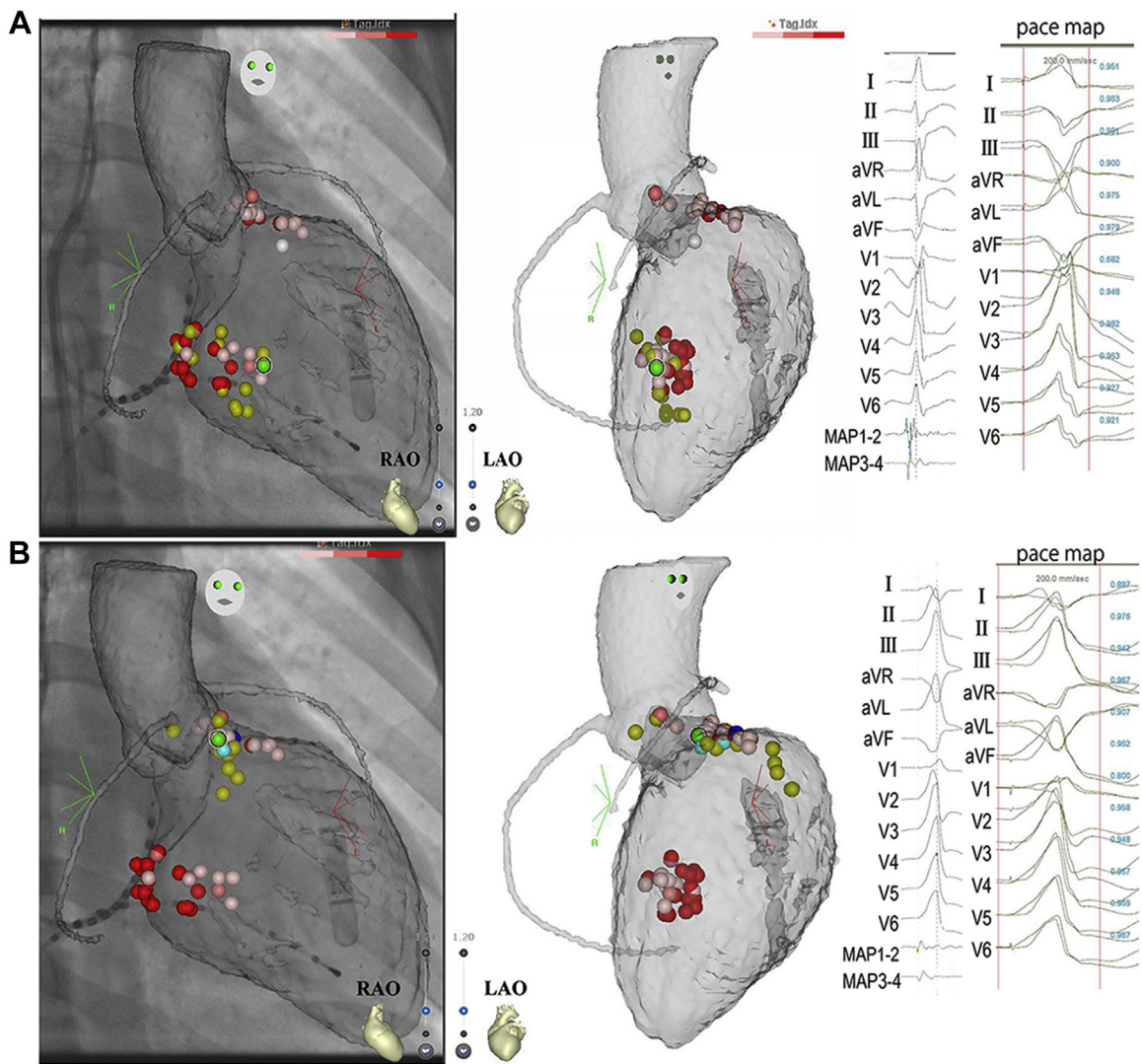
disappeared after the initiation of continuous intravenous flecainide injections. Despite these clinical findings, it was difficult to differentiate whether the syncope was due to epilepsy attacks or lethal arrhythmia, as EEG abnormalities were present. Therefore, we inserted an ICM that confirmed ventricular fibrillation during syncope (Figure 1). In the ICM record, an incremental pattern of PVCs was observed prior to ventricular tachycardia, consistent with her palpitations. Ventricular tachycardia and ventricular fibrillation appeared while climbing the stairs. This lethal arrhythmia spontaneously converted to sinus rhythm without electrical defibrillation. Although she had no family history of sudden cardiac death, we performed trio whole-exome sequencing of her family. Genetic analysis revealed a de novo heterozygous c.12388A>C missense variant (S4130R) in *RyR2*. The minor allele frequency was <0.01 in all public databases.

First, we treated her with optimal pharmacological therapy using 5 mg of bisoprolol fumarate and 200 mg of flecainide, which was found to be highly effective during the drug tolerance test. An ICD was not implanted because its efficacy was reportedly limited and the patient refused it.<sup>7</sup> Although potentially lethal arrhythmic events were frequently induced by low-intensity exercise even after drug administration, sympathetic denervation was unacceptable owing to its aversion to specific complications. Therefore, catheter ablation of reproducible bidirectional PVCs localized in the left ventricular inferoseptal and left ventricular outflow tract areas was performed (Figure 2). An exercise test at 10 METs showed no ventricular tachycardia after successful catheter ablation or optimal pharmacological therapy. The postdischarge exercise restriction was set at 10 METs according to the exercise test.

Following discharge, her rhythm was continuously monitored using ICM. At first, it was difficult for her to recognize precisely how much intensive exercise daily caused the arrhythmia. Furthermore, nonsustained ventricular tachycardia and PVCs were often recorded during light exercises, such as riding a bicycle up a hill or running lightly on level ground (Figure 3). Despite her having palpitations, there were no episodes of syncope. At the outpatient visit, we shared the record with the patient, and the exercise restriction level was modified according to the log data of arrhythmia. The safe threshold of her daily activity could be easily comprehended by confirming the ECG findings, which made her compliant with the exercise restriction. Half a month after discharge, the arrhythmic events decreased in frequency, and her symptoms stabilized. Anticonvulsant agents were gradually reduced; however, special attention was given to the possible recurrence of epilepsy. The patient has been doing well for approximately 2 years, with no problems.

## Discussion

Since patients with pathogenic variants in the *RyR2* often have the same abnormal EEG findings as patients with epilepsy,<sup>8</sup> it would be extremely difficult to distinguish CPVT from epilepsy in early phases, especially during childhood; however, a previous study reported that video EEG monitoring was useful for distinguishing epilepsy from CPVT.<sup>9</sup> It enables continuous and long-acting monitoring of electrical activities in the brain. In addition, continuous ECG monitoring using ICM may be an alternative method because ICM may directly identify the existence of a lethal arrhythmia during syncope, with



**Figure 2** 3D mapping, pace mapping, and activation mapping. Catheter ablation was performed as a therapy for catecholaminergic polymorphic ventricular tachycardia. The red tags indicate ablation points. **A:** 3D mapping, pace mapping, and activation mapping of the green tag of premature ventricular contractions (PVC) arising from the left ventricular inferoseptum. **B:** 3D mapping, pace mapping, and activation mapping of the green PVC tag arising from the left ventricular summit area.

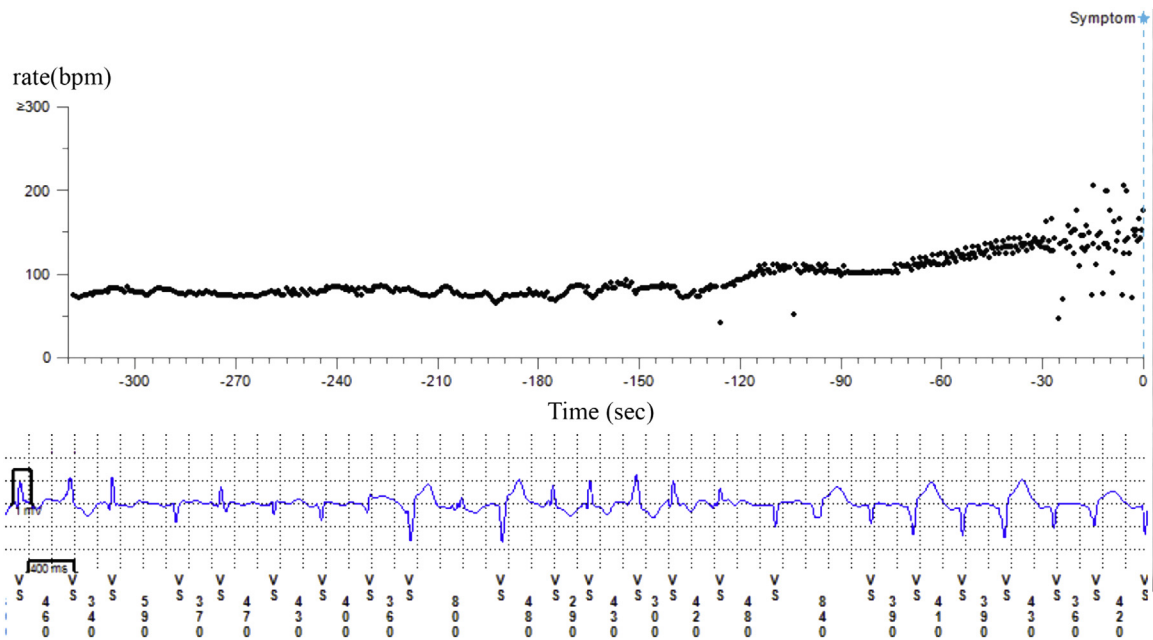
high sensitivity and specificity. ICM may monitor the ECG continuously without interruption; therefore, it can reflect arrhythmias that are closely related to daily life.

According to current guidelines,<sup>1</sup> lifestyle modifications are also recommended in patients with CPVT because exercise causes lethal arrhythmias in accordance with catecholamine release. Therefore, recognizing the frequency of arrhythmias in daily life and compliance with exercise restriction is of paramount importance. Cheung and colleagues<sup>10</sup> argued that the restriction of moderate activity could also be needed to prevent lethal arrhythmias, in addition to avoiding extreme exercise. However, some patients cannot obey the exercise restriction, especially if they are young. In our case, the patient was monitored continuously via ICM after the diagnosis of CPVT. Although she had frequently experienced palpitations while exercising, such as running or cycling, she recorded the episodes with ICM and recognized how much intensive

exercise caused arrhythmia. Simultaneously, physicians easily recognized both symptomatic and asymptomatic events. These benefits were thought to have led to effective management and stability of her condition. Thus, accurate recognition of arrhythmia thresholds and complete removal of triggers are important for the prevention of fatal arrhythmias.<sup>11</sup>

ICD implantation is recommended when CPVT patients experience cardiac arrest or recurrent syncope despite optimal therapy. However, a previous study reported poor efficacy of ICD shocks for triggered arrhythmias.<sup>6</sup> Moreover, an observational study revealed that 42% of CPVT patients who experienced cardiac arrest were younger and did not receive ICD implantation.<sup>7</sup> In our case, the patient, who was a young woman, refused to receive ICD implantation. Further investigation into the indications for ICD in patients with CPVT is required.





**Figure 3** The electrocardiogram from an insertable cardiac monitor during follow-up. The insertable cardiac monitor showed premature ventricular contraction when the patient ran in her daily life after the initiation of beta blockers and flecainide.

With respect to PVC ablation, it is not recommended as the standard therapy according to the current guideline.<sup>1</sup> However, a previous study using a mouse model reported that the Purkinje network was critically associated with arrhythmogenic triggers in CPVT and may be a viable therapeutic target.<sup>12</sup> A single case report showed the effectiveness of PVC ablation for patients with CPVT.<sup>13</sup> Although the maximum available dose of beta blockers was prescribed, beta blockers have been reported to insufficiently prevent sudden cardiac death.<sup>14</sup> In addition, despite refractory syncope and ventricular arrhythmia, she was unable to accept ICD implantation or sympathetic denervation. Therefore, ablation targeting reproducible PVCs and bidirectional VT was performed to further reduce the risk of sudden cardiac death.

The *RYR2* variant detected in this patient was a *de novo* variant with trio analysis. Although this variant has not been reported to date, it is thought to be a pathogenic variant of CPVT. Genetic testing is becoming more widespread and effective for the early and accurate diagnosis of CPVT, especially in cases where clinical diagnosis is difficult.

## Conclusion

The ICM may be practical in aiding physicians in accurately diagnosing and modifying patients' behavior. Moreover, the clinical use of ICM promoted appropriate exercise prescriptions by the physician and compliance in her daily life. To the best of our knowledge, this is the first report demonstrating the effectiveness of ICM as a tool for monitoring patients with CPVT who refused ICD implantation.

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