Recurrent premature ventricular complex–triggered idiopathic polymorphic ventricular arrhythmias in a patient with a structurally normal heart

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Introduction

In this article, we present an intriguing case of recurrent sudden cardiac arrest (SCA) in a young, previously healthy individual, highlighting the diagnostic complexities and evolving scientific insights surrounding idiopathic ventricular arrhythmias. Despite thorough genetic testing and imaging, the initial etiology remained elusive until recurrent polymorphic ventricular tachycardia episodes were linked to premature ventricular complexes. This case also underscores the evolving therapeutic landscape, with interventions ranging from medications to cervical sympathetic denervation (CSD). Genetic evaluation revealed a variant of unknown significance (VUS) in the *CACNA1C* gene, which is most recently known to have a role in the pathophysiology, emphasizing the expanding role of genetics in understanding idiopathic ventricular fibrillation.

Case report

A 31-year-old male patient presented to the hospital after experiencing SCA. The patient had no significant medical history and was found to be in ventricular fibrillation (VF), for which he received 7 shocks and 6 doses of epinephrine until the return of spontaneous circulation was achieved. He reported drinking 4 alcoholic drinks the night before the cardiac arrest. The patient underwent successful implantation of a single-chamber implantable cardioverter-defibrillator (ICD), fully recovered, and enjoyed an active life without medications or interventions until 4 years later, when he received 3 shocks from his ICD (Table 1). The patient reported drinking 6 alcoholic drinks the night before the presentation. Device interrogation revealed 7 episodes of rapid polymorphic ventricular tachycardia (PVT) degenerating to VF. During his hospital stay, the patient continued to experience 20–25 episodes of PVT/VF (Figure 1), and as he was being prepared for transportation to a higher-level care facility,

KEY TEACHING POINTS

- In young patients without coronary artery disease who present with ventricular arrhythmias, it is essential to generate a comprehensive list of potential causes to facilitate an accurate diagnosis.
- Understanding the recommended diagnostic work-up and being aware of the available medical and surgical treatment options for idiopathic ventricular arrhythmias is crucial for optimizing patient care and outcomes.
- It is important to recognize the significance of premature ventricular contractions as triggers for ventricular arrhythmias via the R-on-T phenomenon, as these may be under-recognized contributors to the condition.
- Recent genetic research has shed light on variants of uncertain significance associated with idiopathic polymorphic ventricular tachycardia and ventricular fibrillation, highlighting the evolving understanding of the genetic basis of these arrhythmias and the need for ongoing investigation in this field.

KEYWORDS Ventricular arrhythmias; Sudden cardiac death; ECMO; Holiday heart syndrome; Heart transplant; Surgical cervical sympathetic denervation; CACNA1C gene
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Table 1 Timeline of events

Date	Event
4/19/2015	First cardiac arrest
11/3/2019	Second VT episode with ECMO placement
12/29/2019	Third VT episode with ECMO placement, moderator band ablation
12/28/2021	Fourth VT episode
3/2022	Repeat moderator band ablation, thoracic sympathectomy

ECMO = extracorporeal membrane oxygenation; VT = ventricular tachycardia.

he experienced another SCA that did not respond to multiple ICD shocks. He was initiated on venoarterial extracorporeal membrane oxygenation (ECMO) and transported to another facility.

Tracings of the arrhythmia episodes revealed no evidence of QT-interval prolongation, J-point elevation, or other Brugada abnormality. However, premature ventricular complexes (PVCs) were found on a 6-lead electrocardiogram (ECG), which were suspected to be the trigger for the PVT/VF episodes. During his hospital stay, an echo performed on ECMO support showed an ejection fraction (EF) of 20%. Once ECMO was weaned, repeat echo showed a recovered EF of 60%. *Fluorodeoxyglucose*–positron emission tomography (PET) scan was negative for evidence of sarcoidosis or diffuse myocarditis. He was started on flecainide and diltiazem, and the plan for PVC ablation was deferred, as there were no PVCs seen on telemetry.

The patient presented again 6 weeks later after another syncopal episode and ICD discharge. Device interrogation revealed a PVT terminated by a single shock to sinus rhythm. More episodes led to another venoarterial ECMO cannulation, and quinidine was started. During this admission, episodes of VF were confirmed to be initiated by a monomorphic PVC with a left bundle branch block morphology with a left superior axis, consistent with the origin from the right ventricular moderator band. He was referred for electrophysiology (EP) study and ablation of the triggering PVC. He was brought to the EP lab on ECMO, and extensive ablation along the entirety of the moderator band from the septal insertion to the mid portion of the anterior papillary muscle was performed (Figure 2). The procedure was acutely successful, with no further episodes of PVT or VF, and the patient was discharged home on propranolol.

After a few weeks the patient's EF recovered, and he continued to do well on propranolol. Ten months after the ablation, he was removed from the transplant waiting list. Given frequent ventricular pacing owing to profound sinus bradycardia, the single-chamber ICD was upgraded to a dual-chamber device. He continued without any symptomatic episodes for 2 years, after which he presented following an ICD discharge. He was adherent to the medications and did not drink alcohol or use any illicit drugs. In the emergency department, he had 3 more ICD shocks that required lidocaine infusion followed by a transition to oral quinidine and an increased dose of propranolol. A left stellate ganglion block was successfully performed, and he was relisted for heart transplant evaluation.

Following this admission, the patient sought a second opinion at another hospital to undergo evaluation for potential surgical CSD. There, the heart failure team proposed

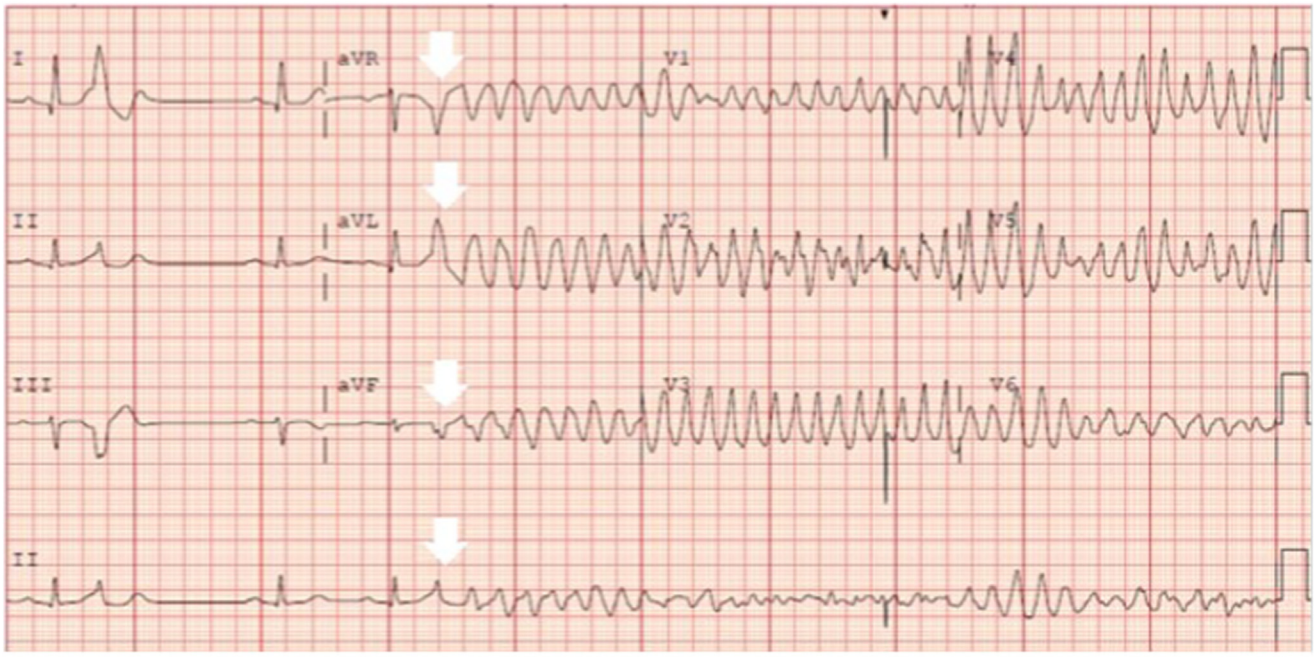

Figure 1 White arrows are pointing out a premature ventricular complex appearing on a T wave, demonstrating the R-on-T phenomenon in an electrocardiogram.

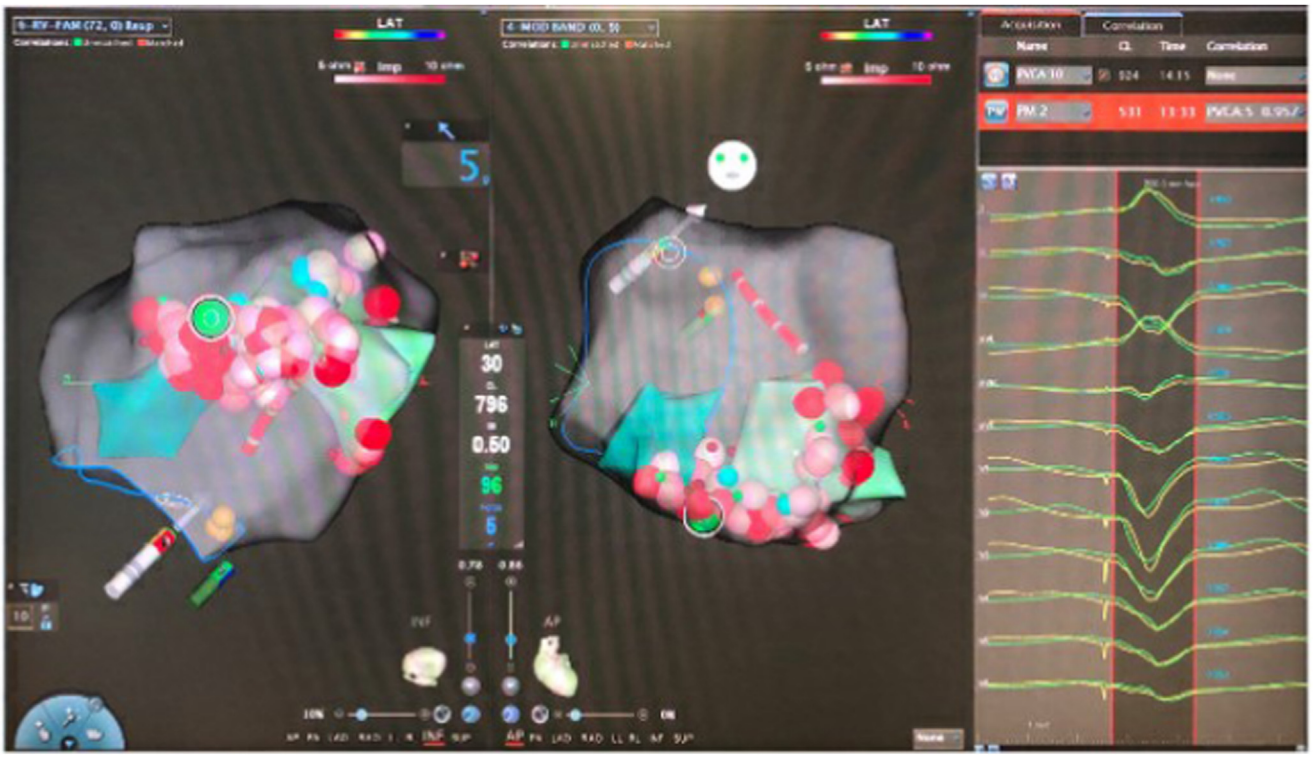

Figure 2 First moderator band ablation. Mapping showing a spontaneous clinical premature ventricular contraction (PVC). This was a 97% match (to a PVC shown in Figure 3) for the pace maps at the mid/lateral aspect of the moderator band.

repeating a sarcoid-protocol PET scan that again did not reveal any signs of sarcoid. A repeat ablation of PVCs arising from the anterolateral papillary muscle was attempted by the EP team, unfortunately, PVCs were seen following the procedure. He was then referred to the thoracic surgery department for CSD, which was uncomplicated. The patient has continued to be arrhythmia-free for the next 10 months.

Differential diagnosis

Initially, this patient was thought to have a prolonged QT-induced ventricular arrhythmia. While ECG on presentation demonstrated prolonged QTc, no other tracing manifested the same finding. Sick sinus syndrome was also briefly considered when he arrived with bradycardia, but this was likely related to SCA rather than any underlying sinoatrial node disease. Brugada syndrome was considered as well but was ruled out, as no J-point or ST elevations were seen on ECG. Lastly, arrhythmogenic cardiomyopathy, specifically arrhythmogenic right ventricular cardiomyopathy and catecholaminergic polymorphic ventricular tachycardia, were investigated, but the inability to induce the ventricular arrhythmia with stress or epinephrine and lack of structural abnormalities seen with multiple imaging modalities, respectively, ruled against these diagnoses.

Investigations

During several admissions, various noninvasive tests and imaging methods were used. Standard 12-lead ECGs helped to rule out many known diagnoses mentioned above. Echocardiograms were used multiple times to look for underlying structural abnormalities, and subsequently to monitor biventricular function and for the development and resolution of heart failure. Cardiac magnetic resonance imaging was used to search for scar tissue in more detail and rule out alternative diagnoses (eg, myocarditis); unfortunately, the study was suboptimal owing to motion artifact. *Fluorodeoxyglucose*-PET scan was performed twice without any findings of sarcoid. Genetic testing for cardiomyopathies and channelopathies was uninformative.

Management

Given the nature of the disease, secondary preventive management approaches were implemented. Initially, the patient was trialed on multiple antiarrhythmic therapies, including lidocaine, amiodarone, flecainide, quinidine, and beta-blockers (esmolol and propranolol), to prevent the recurrence of PVT/VF and lower ectopy burden. PVCs triggering PVT/VF were found to have a minimal coupling interval of 210 ms and a maximum coupling interval of 320 ms. Right ventricular moderator band ablation was performed to isolate the origins of PVCs triggering PVT/VF. Stellate ganglion block was tried as well, with good results, and therefore CSD was recommended by the EP team. After extensive discussion, the patient was listed for cardiac replacement therapy while undergoing evaluation for CSD. A bilateral thoracic sympathectomy was performed to lower sympathetic tone to suppress arrhythmogenesis. Following the procedure, the

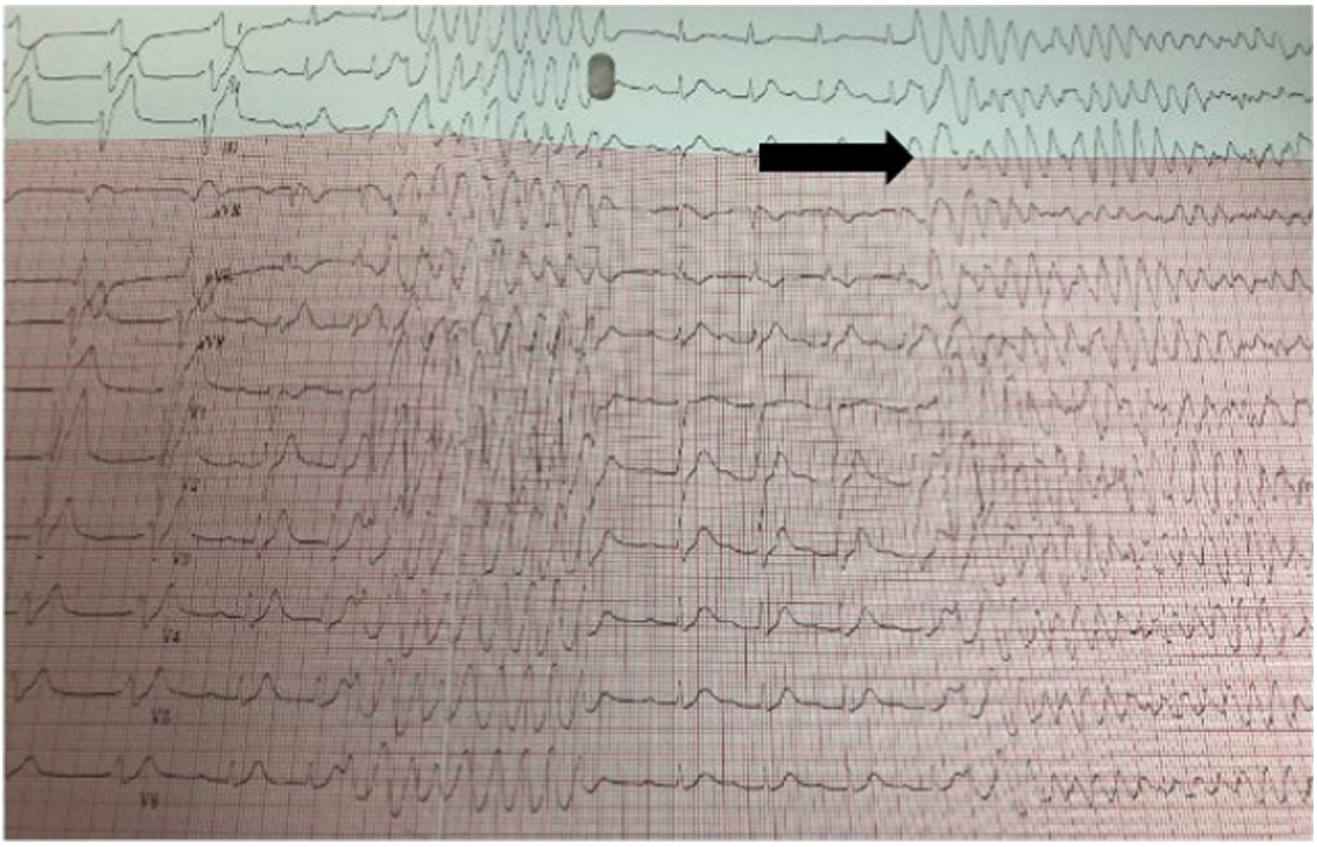

Figure 3 Black arrow showing a premature ventricular contraction with left superior axis triggering an episode of ventricular tachycardia, originating area; the moderator band was later ablated based on this electrocardiogram finding.

patient was continued on quinidine, given the short-coupled PVCs being the culprit.

Discussion

In this case, we present a patient with no past medical history, a structurally normal heart, and no electrocardiographic abnormalities known to have associations with arrhythmogenic syndromes who was found to have drug-refractory recurrent PVT/VF triggered by PVCs and who underwent successful CSD.

As of now the exact underlying mechanism of idiopathic PVT/VF remains unknown. As previously described,[1] clinical and experimental data suggest that the His-Purkinje system plays an important role in the initiation and maintenance of VF.[2] One of the theories of the underlying mechanism suggests that triggered activity—afterdepolarizations or microreentry in the Purkinje cells—could be the electrophysiological culprit of idiopathic PVT/VF. Our patient initially had PVCs consistent with left bundle branch block morphology and superior axis consistent with originating from the right ventricular moderator band. A short coupling interval suggested a Purkinje origin, which was confirmed in the first EP study. Following the initial ablation, more PVCs with various morphologies were seen, making the substrate impossible to control with further ablation.

There are currently 2 treatment approaches for patients diagnosed with idiopathic PVT/VF and frequent ICD shocks; these are antiarrhythmic therapy and ablation. Once an acute electrical storm has been managed, chronic preventive therapy of recurrent PVT/VF takes precedence. Medical management of potential underlying conditions (heart failure, myocardial ischemia) plays a crucial role in the prevention of VT.[3] Pharmacotherapy with amiodarone and propranolol is the first-line therapy for ventricular tachyarrhythmias; if there is recurrence despite medical therapy, catheter ablation of the substrate is the next recommended step. In case of recurrence despite all of these measures, bilateral thoracic sympathectomy may be considered to further lower sympathetic tone.[4] An orthotopic heart transplant should be reserved as the last option.

For the majority of patients, ablation therapy eliminating PVCs provides a long-term cure without any arrhythmia recurrences. Unfortunately, some patients, as in our case, may start to experience a recurrence of PVCs sometimes originating from other areas of the myocardium. As seen in Figure 3, a PVC with left bundle branch block morphology with a superior axis was seen, and therefore EP study was performed. During this study, a PVC almost identical to the previously seen one was induced which had a 97% match for the pace maps at the mid/lateral aspect of the moderator band, and therefore moderator band ablation was performed.

As our patient had a recurrence 2 years later, repeat ablation was considered, but given PVCs of various morphologies coming from various locations of the ventricles seen on electrocardiograms it was decided against the procedure and CSD was recommended. Searching for PVCs in patients with idiopathic PVT/VF is an underappreciated and crucial aspect of appropriate management, as it offers a potential treatment with ablation if feasible.

CSD involves removing part of the cervical stellate and thoracic ganglia, which deliver sympathetic activity to the heart. This procedure can lower the incidence of ventricular arrhythmias and sudden death, making it a viable long-term treatment option for patients with certain arrhythmias, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia.[5] Recent studies have shown success with CSD in patients with underlying structural heart disease or sarcoidosis who have recurrent ventricular arrhythmias.[6,7]

Alcohol consumption was considered a potential trigger for ventricular arrhythmias in the patient's case, as the first 2 episodes of PVT occurred a few hours after drinking 4–6 drinks, which was unusual for him. This is similar to the "holiday heart syndrome," where excessive alcohol use leads to arrhythmias such as atrial fibrillation, atrial flutter, and ventricular tachycardia. In the patient's case, PVCs causing ventricular arrhythmias could have been induced by alcohol use.[8]

Follow-up

The patient was seen in the cardiology genetics center. A VUS was revealed in the *CACNA1C* gene that is associated with Timothy syndrome (long QT syndrome type 8). Unfortunately, the detailed results of the genetic evaluation as the nucleotide and the aminoacidic change are currently not available. Given the recent findings by Pannone and colleagues,[9] it is important to mention that this is a finding of significant clinical relevance, as this seminal paper demonstrated for the first time that both VUS carriers and pathogenic/likely pathogenic carriers have a worse ventricular arrhythmic prognosis in probands with idiopathic VF. It is important to acknowledge the limitations of the ACMG classification when classifying variants as VUS vs pathogenic/likely pathogenic, specifically in cases with idiopathic PVT/VF, as some variants are likely to be underestimated. No other mutations or variants in genes known to cause cardiovascular diseases were identified. The patient was recommended to have all first-degree relatives clinically screened with ECG and a cardiac event monitor. The patient is currently to undergo repeat genetic testing given the above-mentioned findings, to perform further functional analysis of the variant found.

Conclusion

Ventricular arrhythmias remain a lethal cause of SCA and a complete work-up must be done before diagnosing idiopathic ventricular arrhythmias. Appropriate diagnostic work-up of potential trigger events, including PVCs, is crucial, as it has treatment implications. A combination of recurrent PVT/VF or VT storm in the presence of an ICD leads to multiple therapies, potentially causing myocardial stunning and/or acute heart failure. This can potentially escalate to ECMO cannulation or orthotopic heart transplant. Before proceeding with a heart transplant, all potential treatment options should be offered, including recently more understood bilateral CSD that can lead to eliminating PVT/VF recurrences. It is important to remember that living with recurrent ventricular arrhythmias leads often to post-traumatic stress disorder and poor quality of life.

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