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CASE REPORT

ADVANCED

CLINICAL CASE

An Unusual Genetic Observation in a Case of Short-Coupled PVC-Triggered Ventricular Fibrillation

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ABSTRACT

Ventricular fibrillation induced by short-coupled premature ventricular complex is an uncommon cause of cardiac arrest in young individuals with no structural heart disease. The genetic substrate of this condition is heterogeneous and remains incompletely defined. We describe a case of short-coupled premature ventricular complex–triggered ventricular fibrillation with a likely pathogenic variant in the titin (*TTN*) gene. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:101651) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY AND PRESENTATION

A 26-year-old man with an implantable cardioverter-defibrillator (ICD) presented with nonexertional ICD shocks. Clinical examination was unremarkable, without hemodynamic instability or heart failure. ICD interrogation revealed recurrent episodes of ventricular fibrillation (VF), precipitated by a premature ventricular complex (PVC) with a coupling interval <300 milliseconds (**Figure 1**).

LEARNING OBJECTIVES

- To describe the diagnostic approach of short-coupled premature ventricular complex–triggered VF after excluding structural and electrical causes of VF.
- To report a novel, de novo, likely pathogenic *TTN* variant in a case of short-coupled VF.

MEDICAL HISTORY

The patient's medical history was significant for aborted cardiac arrest from VF ~4 years ago. Detailed evaluation, including electrocardiogram, stress test, echocardiography, and cardiac magnetic resonance imaging, did not suggest myocardial ischemia, cardiomyopathy, or obvious electrical disorder. Considering a diagnosis of idiopathic VF, an ICD was implanted. The family history was negative for sudden cardiac death, syncope, or need for implantable cardiac devices.

DIFFERENTIAL DIAGNOSIS

PVC can trigger VF in long QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome, malignant mitral valve prolapse, and ischemia caused

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ABBREVIATIONS AND ACRONYMS

CPVT = catecholaminergic polymorphic ventricular tachycardia

ICD = implantable cardioverter-defibrillator

LQTS = long QT syndrome

sc-PVC = short-coupled premature ventricular complex

TTN = titin

VF = ventricular fibrillation

by obstructive coronary artery disease or intermittent coronary artery spasm.[1,2] Rarely, the VF is precipitated by PVC with a short coupling interval (sc-PVC).[1,3] However, this etiology is diagnosed after exclusion of LQTS, short QT syndrome, Brugada syndrome, CPVT, mitral valve prolapse, myocardial ischemia, and structural heart diseases (ie, hypertrophic, arrhythmogenic, or non-ischemic dilated cardiomyopathy).

INVESTIGATIONS

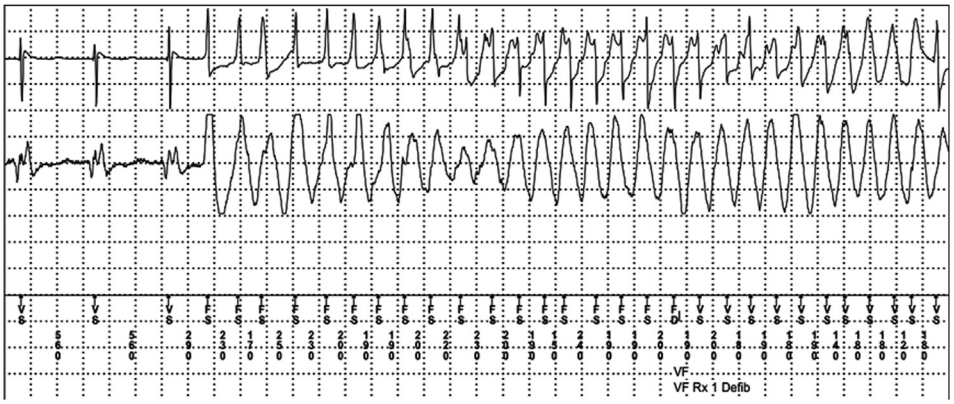
Resting electrocardiogram displayed sinus rhythm, inferior QRS axis, right bundle branch block, a corrected QT interval of 442 milliseconds, and intermittent monomorphic PVC of left bundle branch block morphology in lead V_1, with a left superior axis arising from the preceding T-wave (**Figure 2**). Electrocardiogram with modified high right precordial leads did not display a Brugada pattern.[4] Blood work, including electrolytes and biomarkers of myocardial injury, was normal. Echocardiography excluded any abnormalities in wall thickness, chamber dimension, and ventricular or valvular function. The previous cardiac magnetic resonance imaging was normal without chamber dilatation or late gadolinium enhancement (**Figure 3**). An exercise test did not reveal any ST-segment changes or ventricular arrhythmias, ruling out myocardial ischemia and CPVT, respectively. Normal QT dynamics during exercise and recovery phases further strengthened the exclusion of LQTS. In-hospital continuous electrocardiographic monitoring did not reveal any ST-segment deviation preceding the VF episodes, ruling out coronary vasospasm.

MANAGEMENT

A diagnosis of sc-PVC-triggered VF was considered based on clinical, electrocardiographic, and imaging features. Following initial unsuccessful attempts to suppress VF by using metoprolol, verapamil, or lidocaine, isoproterenol infusion (2 μg/min) suppressed the VF storm. After a 48-hour VF-free period, oral quinine was started (300 mg three times daily) after discontinuation of isoproterenol. A comprehensive cardiomyopathy and channelopathy gene panel analysis (Supplemental Table 1) identified a likely pathogenic variant in the *TTN* gene (c.56647+1G>A). Both parents were asymptomatic; had normal electrocardiogram, echocardiogram, and Holter monitor; and were negative for the abnormal *TTN* variant.

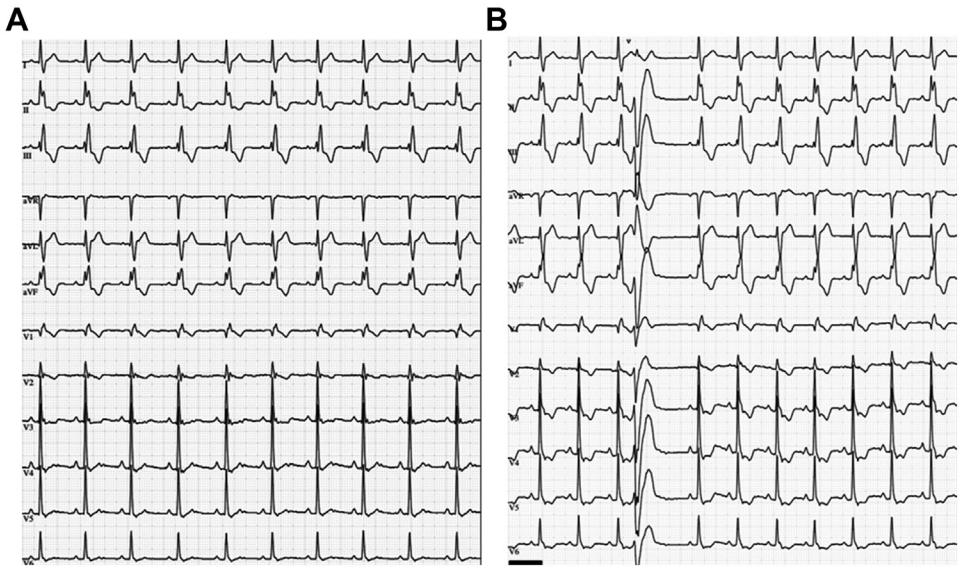
Results of 24-hour Holter monitoring while taking quinine showed isolated, monomorphic PVCs with a PVC burden of 1%. Quinine effectively suppressed VF with a recurrence only after its discontinuation due to the patient experiencing severe gastrointestinal side effects. An electrophysiological study and endocardial activation mapping using the EnSite Precision (Abbott Laboratories) system and high-density mapping catheter (HD Grid catheter, Abbott Laboratories) localized the origin of the culprit PVC at the free wall insertion site of the moderator band (**Figure 4**). Radiofrequency

FIGURE 1 ICD Tracing in VF



Implantable cardioverter-defibrillator (ICD) interrogation showing an episode of ventricular fibrillation (VF) after a short-coupled (290 milliseconds) premature ventricular complex.

FIGURE 2 **12-Lead Electrocardiogram in Sinus Rhythm**



Twelve-lead electrocardiogram showing sinus rhythm and right bundle branch block **(A)** and premature ventricular complex of left bundle branch block morphology **(B)**.

ablations with a 4-mm irrigation tip ablation catheter (43°C, 35 W) effectively eliminated the PVCs.

FOLLOW-UP

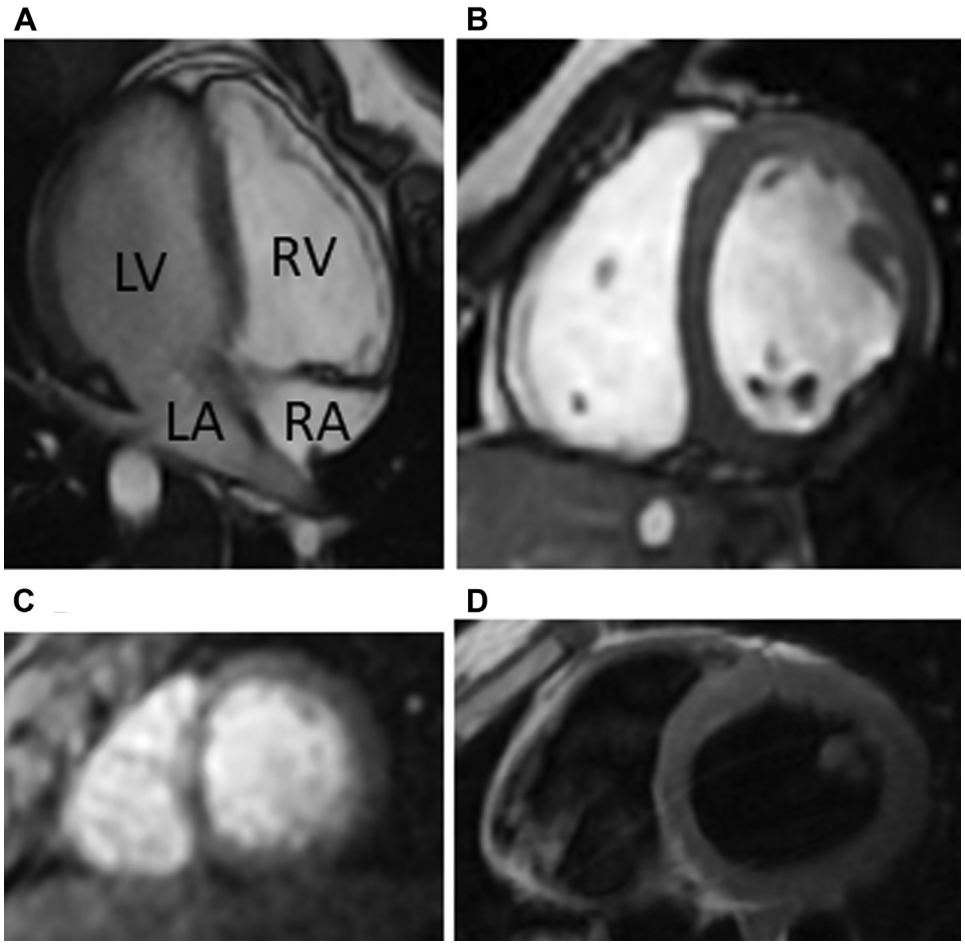
After the successful ablation procedure, the patient has done well without any antiarrhythmic medications. He has remained asymptomatic, and at 6 months' follow-up, 24-hour Holter monitoring did not show any PVC or ventricular arrhythmias.

DISCUSSION

VF triggered by sc-PVC, also known as short-coupled torsades de pointes, is an uncommon cause of sudden arrhythmic death in young individuals without structural heart disease.[3] The baseline electrocardiogram does not suggest any repolarization abnormalities, and the VF is precipitated by a sc-PVC with a coupling interval <300 milliseconds.[1-3] The triggering PVCs usually originate from the His-Purkinje system or the right ventricular outflow tract.[3] Antiarrhythmic drug therapy reportedly has an inconsistent effect in suppressing VF, and ablation of the triggering PVC has emerged as an effective strategy to prevent arrhythmia recurrence.

Although a family history of sudden death is obtained in 25% to 30% of patients, the genetic background seems to be heterogeneous.[3] Variants in DPP6, SEMA3A, CALM1, and RyR2 have been reported in some cases.[5-7] Overexpression of the transient outward current in the Purkinje fibers, transmural heterogeneity of autonomic innervation, and intracellular calcium dysregulation may underlie the malignant ventricular arrhythmias associated with these variants. The genetic analysis of our patient identified a splice site variant (c.56647+1G>A) in the *TTN* gene. This variant is not reported in any population database and is predicted to be damaging by Mutation Taster2 and FATHMM prediction tools. This variant has been reported as "likely pathogenic" in the ClinVar and VarIngDb databases. Likely pathogenic and pathogenic variants in the *TTN* gene have been reported in dilated, hypertrophic, and arrhythmogenic cardiomyopathies.[8] As with other *TTN* splice site variants, the reported variant is also predicted to cause altered splicing, leading to an abnormal truncating protein or variable isoform generation from alternate splicing. The *TTN* mutation site in our patient is located between exons 290 and 291, representing the portion of the protein that

FIGURE 3 Cardiac Magnetic Resonance Imaging



Four-chamber **(A)** and short-axis **(B to D)** views of cardiac magnetic resonance imaging showing normal cardiac chambers without late gadolinium enhancement. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

forms the sarcomere A band. Pathogenic *TTN* variants associated with dilated and arrhythmogenic cardiomyopathy are overrepresented in the A-band region.

The electrocardiogram of our patient displayed right bundle branch block and conduction system abnormalities found in titin cardiomyopathy.[8] His parents were asymptomatic, with no apparent cardiac or skeletal muscle abnormalities, and were negative for the specific *TTN* variant, indicating a likely de novo mutation in the patient (questionable parentage cannot be excluded, although unlikely). Although truncating *TTN* variants occur in cardiomyopathies, an association with sc-PVC-induced VF is not reported. Thus, the identification of a likely pathogenic *TTN* variant in this patient with sc-PVC-induced VF is a novel finding. The titin protein is essential for the sarcomere's assembly and stretch sensing function, and abnormal stretch reportedly causes repolarization heterogeneity.[8,9] The titin protein is also known to regulate the function of the minK subunit of repolarizing potassium channel and distribution of sarcoplasmic ryanodine receptors through interaction with proteins such as telethonin (T-cap protein), obscurin, and ankyrin 1.5.[8] Malfunction of titin may explain cardiac arrhythmia by dysregulation of K^+ current and sarcoplasmic Ca^{2+} handling; however, this theory needs to be experimentally tested.

CONCLUSIONS

This report presents a case of sc-PVC-triggered VF in a young man with no family history of sudden cardiac death. The patient carried a likely pathogenic splice site variant in the *TTN* gene. Neither of his parents exhibited the clinical phenotype or the specific genetic observation. The association between the *TTN* variant and sc-PVC-triggered VF is novel but biologically plausible and requires further association and mechanistic studies. Genetic analysis of this cohort for *TTN* variants and functional analysis of those variants may elucidate the association in the future.

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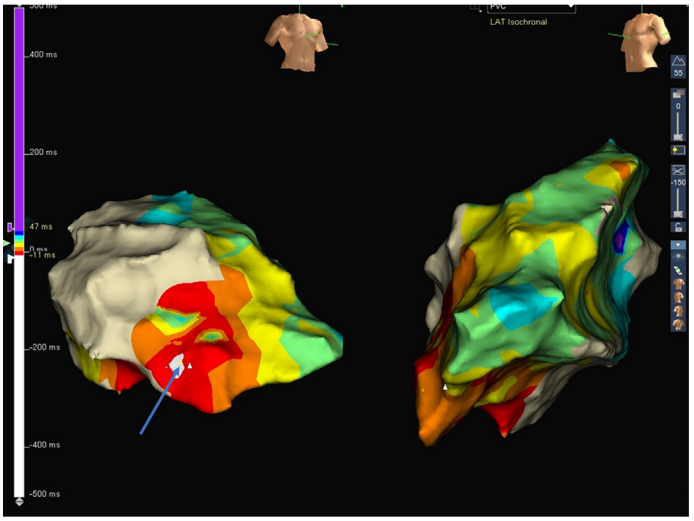
FIGURE 4 **Electroanatomical Mapping of Right Ventricle**



Right ventricular endocardial activation mapping in right anterior oblique **(left panel)** and left anterior oblique **(right panel)** views. Focal origin of premature ventricular complex from free wall insertion site of the moderator band is indicated by **white color (blue arrow)**.

REFERENCES

1. Leenhardt A, Glaser E, Burguera M, Nürnberg M, Maison-Blanche P, Coumel P. Short-coupled variant of torsade de pointes. A new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias. *Circulation*. 1994;89:206-215.

2. Von Alvensleben JC, Etheridge SP, Viskin S, Collins KK. Short-coupled premature ventricular beats leading to ventricular fibrillation in a young patient: a sudden arrhythmia death syndrome case report and literature review. *HeartRhythm Case Rep*. 2020;6:815-818.

3. Haïssaguerre M, Shoda M, Jaïs P, et al. Mapping and ablation of idiopathic ventricular fibrillation. *Circulation*. 2002;106:962-967.

4. Gray B, Behr ER. New insights into the genetic basis of inherited arrhythmia syndromes. *Circ Cardiovasc Genet*. 2016;9:569-577.

5. Cheung JW, Meli AC, Xie W, et al. Short-coupled polymorphic ventricular tachycardia at rest linked to a novel ryanodine receptor (RyR2) mutation: leaky RyR2 channels under non-stress conditions. *Int J Cardiol*. 2015;180:228-236.

6. Ten Sande JN, Postema PG, Boekholdt SM, et al. Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm*. 2016;13:905-912.

7. Nakano Y, Chayama K, Ochi H, et al. A nonsynonymous polymorphism in semaphorin 3A as a risk factor for human unexplained cardiac arrest with documented ventricular fibrillation. *PLoS Genet*. 2013;9:e1003364.

8. Gigli M, Begay RL, Morea G, et al. A review of the giant protein titin in clinical molecular diagnostics of cardiomyopathies. *Front Cardiovasc Med*. 2016;3:21.

9. Healy SN, McCulloch AD. An ionic model of stretch-activated and stretch-modulated currents in rabbit ventricular myocytes. *Europace*. 2005;7(suppl 2):128-134.

KEY WORDS genetic disorders, secondary prevention, ventricular fibrillation

APPENDIX For a supplemental table, please see the online version of this paper.