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CASE REPORT

CLINICAL CASE

RYR1 Pathogenic Variant in a Patient With Overlapping Features of Brugada Syndrome and Arrhythmogenic Cardiomyopathy

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ABSTRACT

BACKGROUND Brugada syndrome (BrS) and arrhythmogenic cardiomyopathy (ACM) may overlap clinically, but shared mechanisms remain unclear. *RYR1* mutations have not been previously linked to these arrhythmia syndromes.

CASE SUMMARY A 32-year-old man with a family history of BrS presented with palpitations and positional ventricular tachycardia. Ajmaline testing unmasked a diagnostic type 1 BrS electrocardiographic pattern. Cardiac magnetic resonance showed subtle right ventricular dyskinesia and focal left ventricular fibrosis, meeting borderline ACM criteria. Electrophysiological study showed noninducible ventricular arrhythmias, but premature ventricular contractions were reproducibly provoked in the left-lateral position. After shared decision-making, an implantable cardioverter-defibrillator was implanted for primary prevention. Genetic testing revealed a pathogenic truncating *RYR1* variant (p.Arg2920*).

DISCUSSION This case illustrates a novel association of *RYR1* mutation with overlapping BrS-ACM features. Shared connexome and calcium-handling abnormalities may underlie this phenotype.

TAKE-HOME MESSAGES *RYR1* mutations may contribute to overlapping BrS-ACM phenotypes. Careful imaging, provocative testing, and genetic assessment can guide management. (JACC Case Rep. 2026;■:107528) © 2026 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 OF PRESENTATION

A 32-year-old man with a family history of Brugada syndrome (BrS) was referred to our hospital for further evaluation of episodes of palpitations and dizziness attributed to salvos of ventricular arrhythmias. His brother had been diagnosed with BrS and received an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death. Both parents had negative ajmaline testing and no spontaneous Brugada-type pattern on baseline electrocardiogram (ECG). Genetic testing

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ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

BrS = Brugada syndrome

ECG = electrocardiogram

ICD = implantable cardioverter-defibrillator

PVC = premature ventricular contraction

RVOT = right ventricular outflow tract

RyRs = ryanodine receptors

was recommended to the family, but they declined. On admission, physical examination and 12-lead ECG were unremarkable without any features of cardiomyopathy or channelopathy (Figure 1). Transthoracic echocardiography showed normal cardiac structure and function. Ambulatory monitoring revealed numerous salvos of ventricular tachycardia (VT) that were consistently elicited in the left lateral body position (Figure 2). Premature ventricular contractions (PVCs) recorded on 12-lead ECG displayed a left bundle branch block morphology with a left superior axis, suggesting an origin from the inferior right ventricular inflow tract (Figure 3).

PAST MEDICAL HISTORY

The patient had no previous cardiovascular or systemic disease and was not taking any medications. He denied syncope but described intermittent palpitations occurring during physical activity.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included BrS due to the positive family history of BrS in a first-degree relative, and arrhythmogenic right ventricular cardiomyopathy (ARVC) given the morphology of the ventricular arrhythmias. Idiopathic VT arising from the right ventricular inflow or outflow tract was also considered. Because the ventricular arrhythmias were consistently triggered in the left lateral position, positional ventricular ectopy was included in the differential. Other inherited arrhythmia syndromes and cardiomyopathies remained possible until further testing clarified the diagnosis.

TAKE-HOME MESSAGES

- *RYR1* mutations can be linked to unusual ventricular arrhythmia syndromes with overlapping BrS and borderline ARVC features.
- Thorough assessment with imaging, genetic testing, and electrophysiological evaluation is important to guide treatment.

INVESTIGATIONS

Given his family history, a sodium channel blocking test with ajmaline was performed and revealed a diagnostic type 1 Brugada electrocardiographic pattern (Figure 4).

Cardiac magnetic resonance demonstrated normal biventricular volumes and ejection fraction, with 2 small dyskinetic areas located in the subtricuspid region and the right ventricular outflow tract (RVOT). In addition, focal subepicardial fibrosis was identified in the basal inferior left ventricular wall (Figure 5).

Genetic testing identified a heterozygous variant in the *RYR1* gene. This variant involves a single nucleotide substitution at position 8,758, resulting in the replacement of arginine with a premature stop codon at position 2,920 of the protein (p.Arg2920*). The truncated protein is expected to be nonfunctional, and the variant was classified as pathogenic. Genomic DNA was analyzed using a solution-based target enrichment approach (KAPA Hereditary Disease Panel; Roche) followed by next-generation sequencing on the DNBSEQ-G400 platform (MGI),

VISUAL SUMMARY **Timeline of Clinical Evaluation, Diagnostic Testing, and Management in the Patient**

Time Point	Clinical Events
Initial presentation (day 1)	Patient referred for evaluation of palpitations and dizziness. Physical examination, baseline ECG, and echocardiogram were normal. Ambulatory monitoring initiated.
Day 1	Ambulatory monitoring showed frequent PVCs and salvos of ventricular tachycardia reproducibly triggered in the left lateral body position.
Day 1	PVC morphology (LBBB with left superior axis) identified, suggesting right ventricular inflow tract origin.
Day 2	Ajmaline provocation test performed due to family history; diagnostic type 1 Brugada pattern unmasked.
Day 3	CMR revealed normal biventricular function with small dyskinetic RV regions and focal subepicardial LV fibrosis, consistent with borderline ARVC criteria.
Day 4	Electrophysiological study conducted. Normal conduction intervals; PVCs triggered by left lateral positioning; no inducible sustained VT/VF.
Day 7	After shared decision-making, an ICD was implanted for primary prevention of sudden cardiac death.
Day 58	Genetic analysis detected a disease-causing truncating mutation in *RYR1* (p.Arg2920).*
Follow-up (day 90)	Patient remained asymptomatic with no sustained arrhythmias or ICD therapies.

ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricular; PVC = premature ventricular contraction; RV = right ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

FIGURE 1 12-Lead Electrocardiogram on Admission

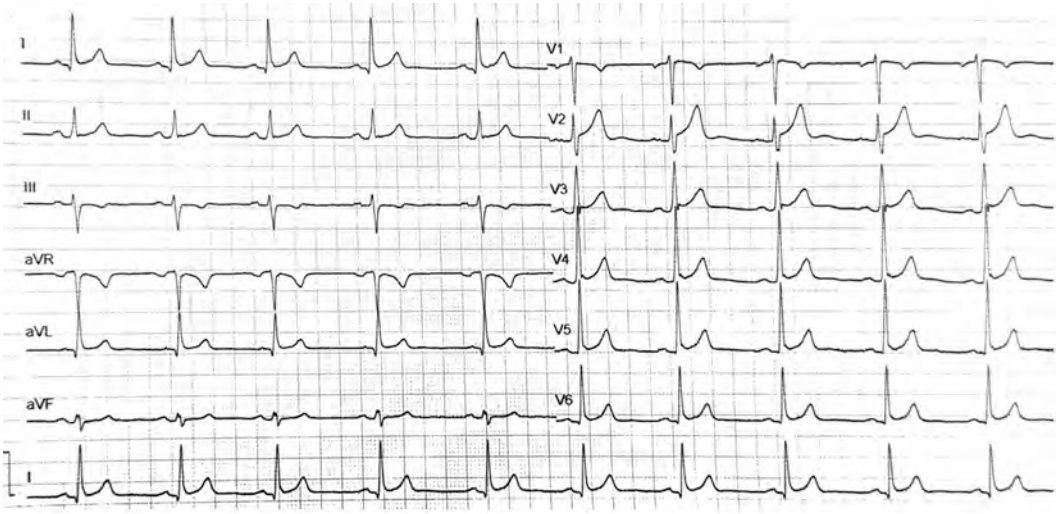


FIGURE 2 Ambulatory Monitoring Revealed Numerous Salvos of Ventricular Tachycardia Elicited in the Left Lateral Body Position

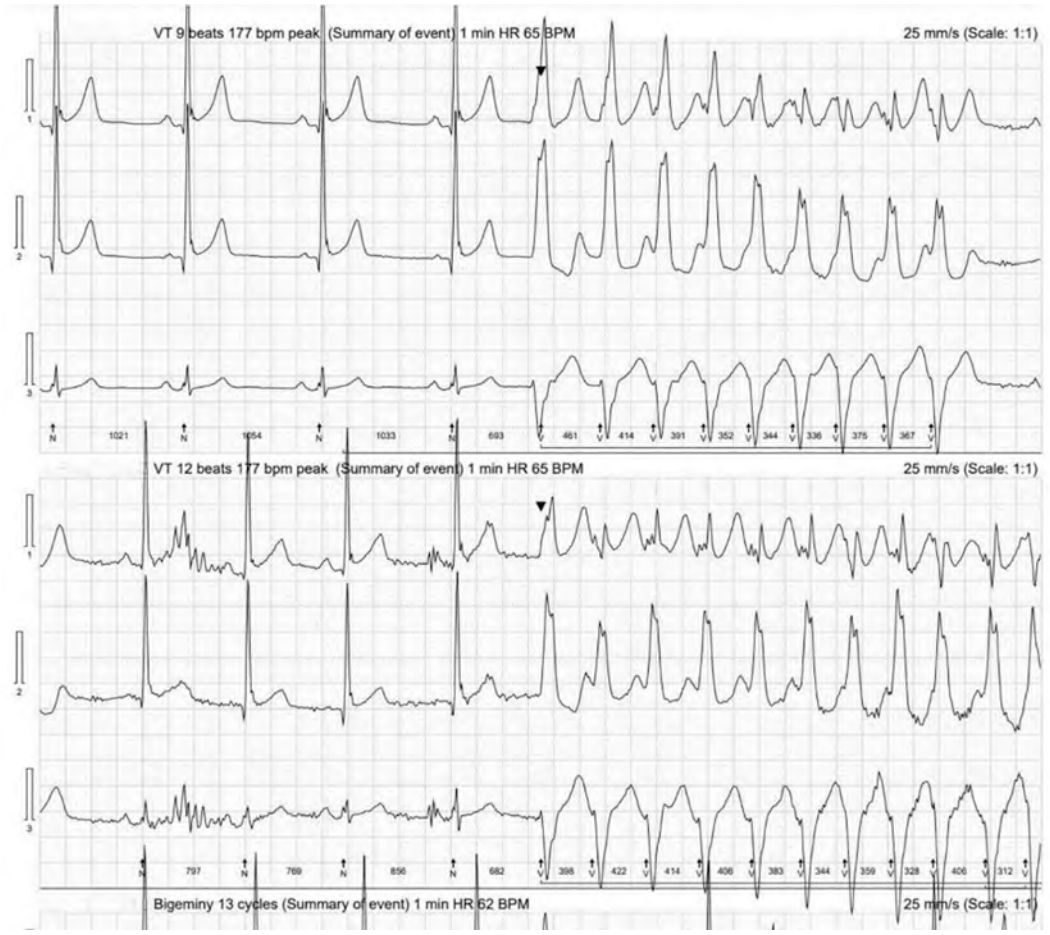
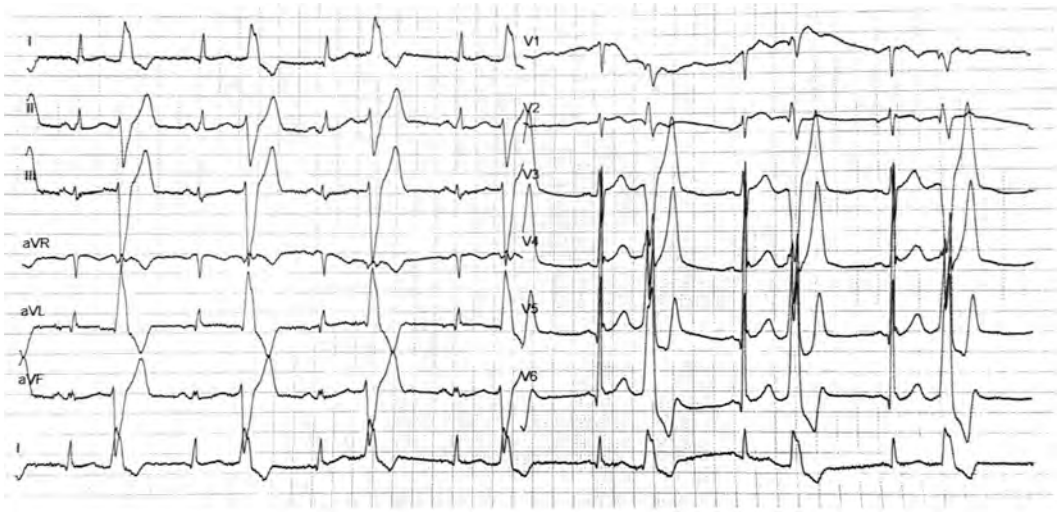


FIGURE 3 Morphology of Premature Ventricular Contractions on 12-Lead Electrocardiogram



with reads aligned to the GRCh37 reference genome. The assay targeted 294 genes associated with inherited cardiac disorders, achieving a mean coverage of 233× with 100% of targeted regions sequenced at ≥20× depth. Variant interpretation was performed according to American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines, and all clinically significant findings were confirmed by Sanger sequencing (SeqStudio Genetic Analyzer; Thermo Fisher Scientific). Large genomic rearrangements were assessed using SeqPilot software (JSI Medical Systems GmbH) and verified by multiplex ligation-dependent probe amplification (MLPA) (MRC Holland) (Figure 6). An electrophysiological study was performed for further risk stratification. Baseline AH (conduction time from low right atrial electrogram to His bundle electrogram) and HV (conduction time from His bundle electrogram to earliest ventricular activation) intervals and the corrected sinus node recovery time were within normal limits. During the study, the left lateral body position again triggered PVCs. Programmed ventricular

FIGURE 4 Ajmaline Challenge Unmasking the Diagnostic Type 1 Electrocardiographic Pattern of Brugada Syndrome

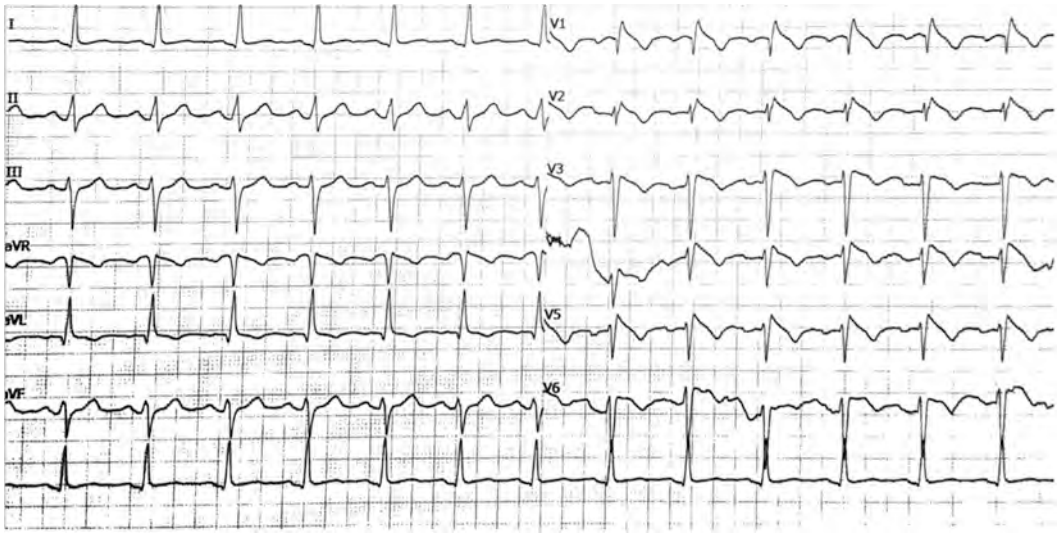
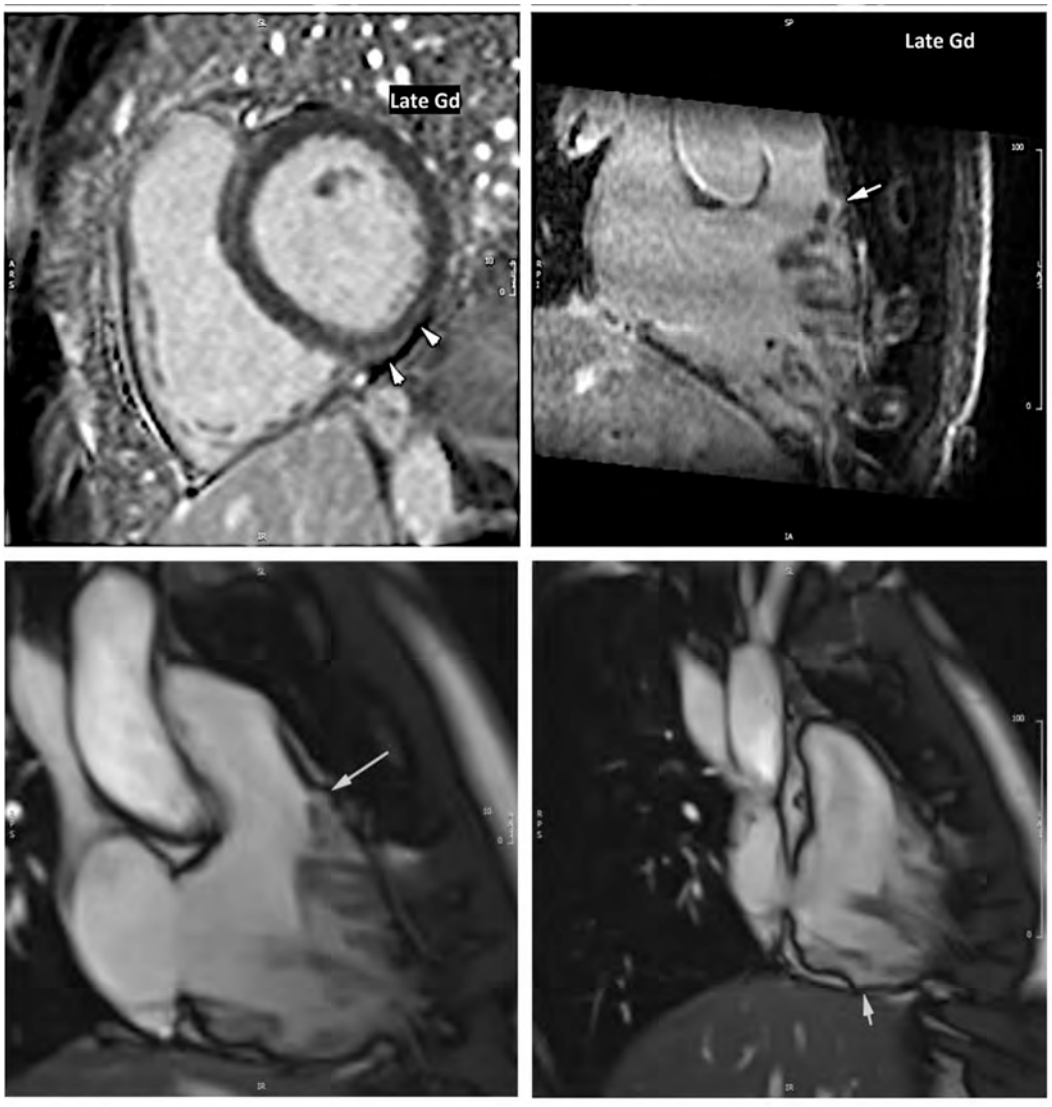


FIGURE 5 Cardiac Magnetic Resonance Findings Demonstrating Focal Fibrosis and Right Ventricular Dyskinesia



Cardiac magnetic resonance demonstrating focal subepicardial fibrosis in the basal inferior wall of the left ventricle (double arrows) and 2 small dyskinetic areas at the subtricuspid region and at the outflow tract of the right ventricle (single arrows). Gd = gadolinium.

stimulation did not induce sustained VT or ventricular fibrillation.

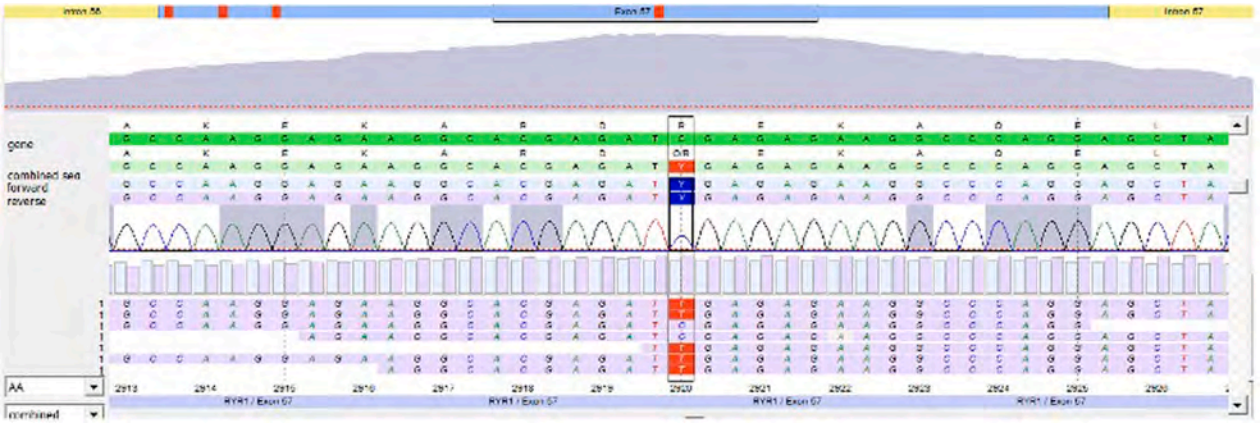
MANAGEMENT

Risk stratification was guided by the cardiac imaging. The patient was started on bisoprolol 2.5 mg daily for symptomatic control. After discussion of the findings and treatment options, an ICD was implanted for primary prevention of sudden cardiac death. The decision was guided by cumulative clinical risk, including a drug-induced type 1 Brugada electrocardiographic pattern, a positive family history in a first-degree relative, recurrent symptomatic ventricular arrhythmias, and subtle structural abnormalities on cardiac magnetic resonance; the *RYR1* variant was not considered an independent indication.

OUTCOME AND FOLLOW-UP

During hospitalization, PVCs continued to be reproducibly triggered in the left-lateral position, and episodes of nonsustained VT occurred despite beta-blocker therapy. The patient recovered well after

FIGURE 6 Sanger Sequencing Confirmation of the Heterozygous *RYR1* c.8758C > T Variant (p.Arg2920*) Producing a Premature Termination Codon in Exon 57



ICD implantation. At 90-day follow-up, he remained asymptomatic, with no sustained ventricular arrhythmias and no ICD therapies recorded.

DISCUSSION

Three key findings emerge from this case report: 1) salvos of VT elicited by the left-lateral recumbent position are uncommon; 2) features of BrS and ARVC may overlap, making the final diagnosis challenging; and 3) *RYR1* gene mutations have not previously been reported in patients with ventricular arrhythmias and overlapping features of BrS and borderline arrhythmogenic cardiomyopathy.

PVCs or VT triggered by specific body positions are rare.[1] Body position can also be arrhythmogenic in patients with premature atrial contractions.[2] Changes in mechanical stretch and autonomic tone may underlie this phenomenon. In the present case, no specific structural or anatomical abnormalities explaining the positional ventricular arrhythmias were identified on cardiac magnetic resonance or during electrophysiological study. Changes in ventricular loading conditions, mechanical stretch, or autonomic tone may therefore underlie this phenomenon; however, the precise mechanism remains speculative.

According to the 2024 European Task Force consensus report on the diagnosis of arrhythmogenic cardiomyopathy,[3] our patient met 1 major and 1 minor criterion, resulting in a "borderline" ARVC diagnosis. Major right ventricular dyskinesia and minor left ventricular subepicardial fibrosis supported borderline disease, with right ventricular arrhythmias suggesting an early electrical phase despite absent diagnostic electrocardiographic features. Based on the 2022 European Society of Cardiology guidelines for the management of ventricular arrhythmias and the prevention of sudden cardiac death,[4] BrS should be considered in patients with an induced type 1 Brugada pattern and a family history of BrS.

BrS is a complex arrhythmogenic disorder characterized by electrical and microstructural abnormalities, predominantly affecting the epicardial layer of the RVOT. Histopathologic studies have shown fibrosis, fatty infiltration, inflammatory cell infiltration, and reduced expression of gap junction proteins—particularly connexin-43—mainly at the RVOT epicardium in patients with BrS.[5] These structural alterations create an arrhythmogenic substrate that promotes reentry and the development of ventricular fibrillation. Epicardial substrate-guided ablation targeting these areas can normalize the Brugada electrocardiographic pattern and eliminate inducible ventricular arrhythmias, supporting the concept of BrS as an epicardial cardiomyopathy.[5]

A sodium channel blocker test can induce the diagnostic coved-type BrS electrocardiographic pattern in up to 16% of patients diagnosed with arrhythmogenic cardiomyopathy. Imaging studies further show that subtle cardiac structural abnormalities are present in many BrS patients. Right ventricular wall motion abnormalities are observed in up to 71% of patients with Brugada electrocardiographic patterns, and localized ARVC-like structural changes are found in 16%.[6] Notably, 8% of patients fulfill criteria for both BrS and ARVC.[6]

A shared pathophysiological basis for BrS and arrhythmogenic cardiomyopathy may relate to "connexome" defects.[7] The cardiac intercalated disc contains a highly integrated network—the connexome—consisting of desmosomes, fascia adherens junctions, gap junctions, and voltage-gated sodium

channels, which work together to maintain electrical conduction, excitability, and mechanical coupling.[7] Disruption of any component can impair sodium channel function, particularly the Nav1.5 α-subunit encoded by *SCN5A*.[7]

The ryanodine receptors (RyRs) are intracellular calcium-release channels. RyR1 is the primary isoform in skeletal muscle, whereas RyR2 predominates in cardiomyocytes.[8] RyR1 mediates voltage-induced Ca^{2+} release and skeletal muscle-type excitation-contraction coupling. Mutations in *RYR1* cause several muscle disorders, including malignant hyperthermia, exertional rhabdomyolysis, central core disease, multiminicore disease, and certain periodic paralyzes, findings that were not present in our patient.[8] Although *RyR1* is expressed at low levels in cardiomyocytes, its expression increases in diseased myocardium. Increased expression of isoform 1 of the sarcoplasmic reticulum Ca^{2+} release channel could contribute to impaired excitation-contraction coupling in human heart failure.[9] Common *RYR1* variants have also been associated with left ventricular hypertrophy.[10]

Based on these observations, it is conceivable that *RYR1* variants may contribute to arrhythmogenic mechanisms through altered calcium handling and disruption of the cardiac connexome, potentially accounting for the overlapping features of BrS and arrhythmogenic cardiomyopathy observed in this patient. Abnormal diastolic calcium release may promote delayed afterdepolarizations, leading to PVCs and VT. However, the identified *RYR1* variant may also represent an incidental finding, and no direct causal relationship can be established. To date, no experimental or clinical studies have demonstrated an association between *RYR1* variants and BrS or borderline arrhythmogenic cardiomyopathy. Further functional studies are required to better define its potential role.

CONCLUSIONS

This case describes a patient with features of both BrS and borderline arrhythmogenic cardiomyopathy, whose ventricular arrhythmias were triggered by body position. A pathogenic *RYR1* mutation was found, which may play a role in abnormal calcium handling and structural conduction abnormalities. Diagnosis and management relied on careful imaging, provocative testing, and genetic evaluation, leading to ICD implantation and treatment with a beta-blocker.

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KEY WORDS cardiomyopathy, genetic disorders, ventricular tachycardia