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RHYTHM DISORDERS AND ELECTROPHYSIOLOGY

CLINICAL CASE

Imagenomics and Ventricular Arrhythmia

The Scar, The Channel, The Variant

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ABSTRACT

BACKGROUND Imagenomics is an emerging clinical framework that combines advanced imaging and genetic profiling to refine risk stratification and advance precision medicine in the management of ventricular arrhythmias.

CASE SUMMARY A 43-year-old woman presented with palpitations and presyncope. Ambulatory electrocardiogram revealed frequent premature ventricular contractions and nonsustained ventricular tachycardia, consistently initiated by a premature ventricular contraction with distinct morphology. Cardiac magnetic resonance scan identified a nonischemic scar in the basal inferolateral segment of the left ventricle, with a protected conduction corridor of heterogeneous tissue within the border zone. Electroanatomic mapping confirmed a critical isthmus that was anatomically colocalized with the cardiac magnetic resonance–defined corridor. Programmed ventricular stimulation induced sustained monomorphic ventricular tachycardia that degenerated into ventricular fibrillation, necessitating implantable cardioverter-defibrillator placement. Genetic analysis revealed a heterozygous, likely pathogenic *TECRL* variant, associated with catecholaminergic polymorphic ventricular tachycardia type 3.

DISCUSSION This case highlights a composite arrhythmogenic mechanism shaped by myocardial scar substrate, protected conduction architecture, and inherited susceptibility. (JACC Case Rep. 2025;30:104938) © 2025 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 43-year-old woman was referred for evaluation of fatigue, palpitations, and presyncope persisting over the preceding year.

PAST MEDICAL HISTORY

The patient had experienced a mildly symptomatic SARS-CoV-2 infection approximately 12 months earlier. She had no known cardiovascular disease or

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ABBREVIATIONS AND ACRONYMS

3D = three-dimensional

CMR = cardiac magnetic resonance

CPVT3 = catecholaminergic polymorphic ventricular tachycardia type 3

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricle

PVC = premature ventricular contraction

RBBB = right bundle branch block

VT = ventricular tachycardia

conventional risk factors. There was no family history of sudden death, cardiomyopathies, or inherited arrhythmia syndromes.

DIFFERENTIAL DIAGNOSIS

Our differential diagnosis included arrhythmic disorders, myocarditis, non-ischemic cardiomyopathy, and long COVID syndrome.

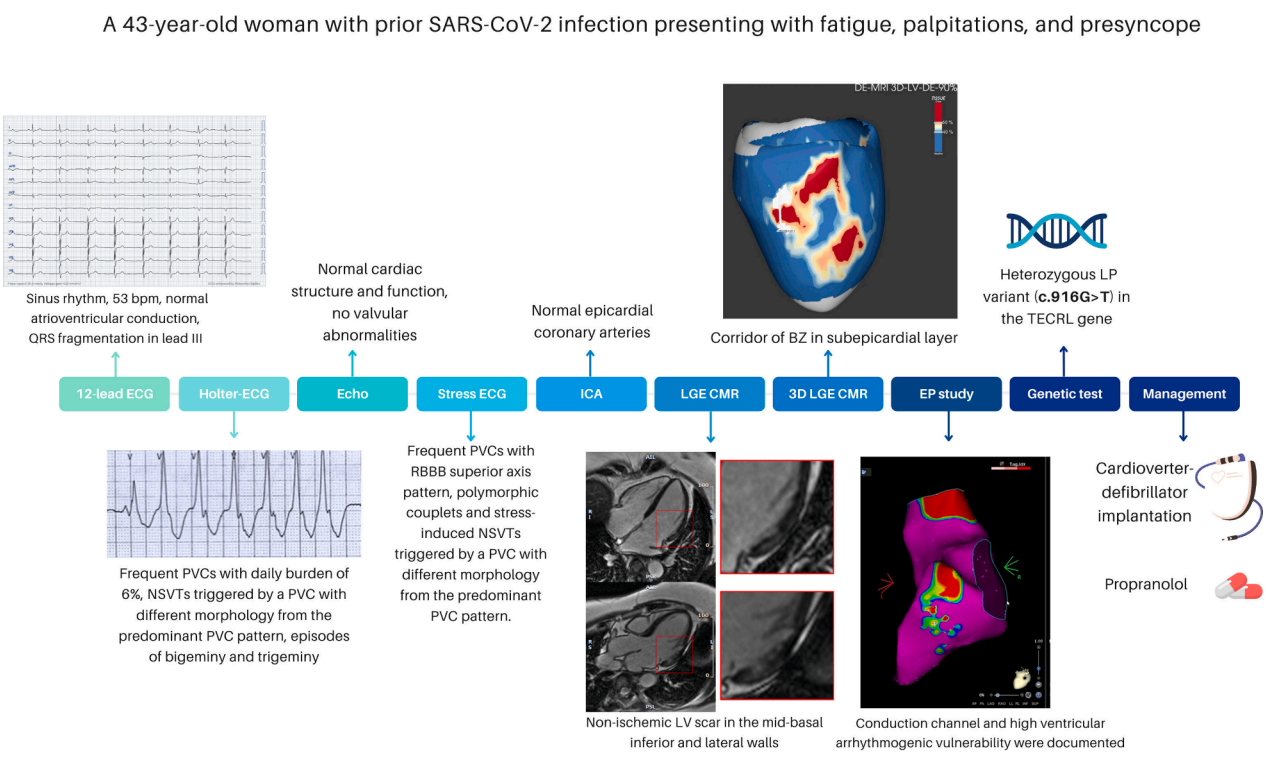
INVESTIGATIONS

Resting 12-lead electrocardiogram (**Figure 1**) showed sinus rhythm at 53 beats/min, normal atrioventricular conduction, and QRS fragmentation in lead III, without additional abnormalities. Physical examination and routine laboratory work-up were unremarkable.

TAKE-HOME MESSAGES

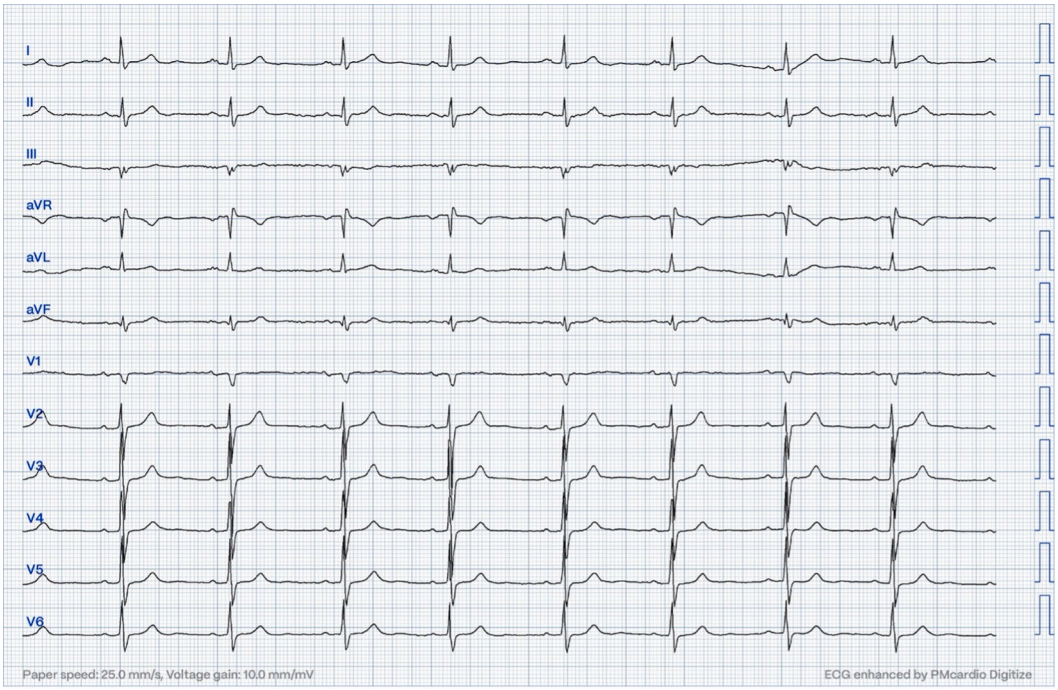
- In patients with nonsustained VT, a first PVC with distinct morphology from subsequent beats should prompt suspicion of a re-entrant mechanism and guide targeted investigation for concealed myocardial scar and conduction channels.
- Advanced CMR imaging with postprocessing scar architecture analysis enables identification of conduction corridors within heterogeneous tissue, uncovering critical substrates for re-entrant ventricular arrhythmias beyond conventional imaging metrics.
- Integrating structural imaging, electroanatomic mapping, and genetic profiling provides a comprehensive framework for arrhythmic risk stratification and personalized clinical decision-making in complex ventricular arrhythmia syndromes.

VISUAL SUMMARY **Imagenomics and Ventricular Arrhythmia**



BZ = border zone; EP = electrophysiological; ICA = invasive coronary angiography; LGE CMR = late gadolinium enhancement cardiac magnetic resonance; LP = likely pathogenic; LV = left ventricle; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; RBBB = right bundle branch block; TECRL = trans-2,3-enoyl-CoA reductase-like; VT = ventricular tachycardia. Image created with Canva (Canva Pty Ltd).

FIGURE 1 Standard 12-Lead Electrocardiogram

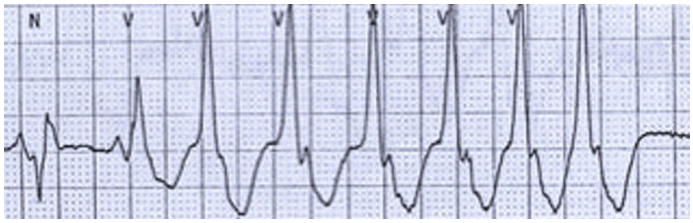


Transthoracic echocardiography revealed normal cardiac anatomy and preserved biventricular function. Ambulatory 12-lead electrocardiogram documented a premature ventricular contraction (PVC) burden of 6% (1,576 PVCs/24 h), with a predominant morphology of right bundle branch block (RBBB). Nonsustained episodes of ventricular tachycardia (VT) were consistently initiated by PVCs, with a morphology distinct from the predominant PVC pattern (**Figure 2**). Additional findings included frequent episodes of ventricular bigeminy and trigeminy. Exercise testing—performed on bisoprolol 2.5 mg once daily—elicited frequent RBBB/superior axis PVCs and polymorphic couplets, and testing was prematurely terminated owing to stress-induced monomorphic nonsustained VT with an RBBB/superior axis configuration, similarly triggered by a PVC of different morphology. Coronary angiography excluded obstructive or aberrant epicardial coronary artery disease.

A first cardiac magnetic resonance (CMR) study was nondiagnostic owing to suboptimal image quality, primarily related to motion artifacts and poor breath-hold performance. Bisoprolol therapy was initiated. Ancillary tests excluded neuromuscular and autoimmune disorders. Because of symptom persistence, a subsequent CMR scan was performed on a 3-T platform (Prisma, Siemens Medical Solutions) using a free-breathing (8 averages), motion-corrected, phase-sensitive inversion-recovery late gadolinium enhancement (LGE) sequence and a free-breathing, three-dimensional (3D) whole-heart LGE sequence enabling isotropic high-resolution scar characterization. Ventricular volumes, wall thickness, and left ventricular (LV) mass were within normal limits. Biventricular systolic function was preserved (LV ejection fraction: 60%, right ventricular ejection fraction: 55%) (Videos 1 to 4). A subepicardial scar of the midbasal inferolateral LV wall was identified (**Figure 3**).

The 3D LGE dataset was postprocessed using ADAS 3D LV software (Galgo Medical). A 9-layer concentric surface mapping approach (10%-90% of myocardial wall thickness) was applied, coupled with a color-coded pixel signal intensity algorithm for advanced tissue characterization and scar architecture analysis. Myocardial regions were classified as core zone (>60% ± 5% of maximum pixel signal intensity), border zone (40% ± 5% to 60% ± 5%), and healthy myocardium (<40% ± 5%), in accordance with validated thresholds. Total scar mass was 21.2 g, with a heterogeneity index (border zone mass/scar mass) of 83%, indicating a predominance of

FIGURE 2 Nonsustained Ventricular Tachycardia Recorded on 24-Hour Holter Electrocardiogram



The first beat exhibits a morphology distinct from the subsequent beats within the tachycardia sequence, a pattern suggestive of a scar-related re-entrant mechanism.

intermediate signal intensity tissue within the scar. A conduction corridor composed of border zone tissue was identified (Figure 4), with a computed mass of 0.369 g. The corridor exhibited medium protectedness, defined by partial insulation from surrounding dense scar and anatomical boundaries. This structural configuration corresponded to a continuous path of viable tissue within the scar, consistent with a potential anatomical substrate for re-entrant ventricular arrhythmia.

MANAGEMENT

The 3D LGE CMR reconstructions were reviewed by the electrophysiology team before the procedure and were used to guide the intraprocedural mapping strategy. The patient subsequently underwent an electrophysiological study with programmed ventricular stimulation.[1] Electroanatomic mapping confirmed low-voltage areas localized to the basal inferior wall with significant epicardial extension, consistent with the substrate identified on 3D LGE CMR. A critical isthmus was identified within these areas, anatomically colocalized with the conduction corridor previously delineated by CMR, reinforcing the correspondence between structural scar architecture and electrophysiological substrate (Figure 5). High arrhythmogenic vulnerability was documented, with induction of sustained monomorphic VT with a RBBB configuration and superior axis—matching the morphology observed during exercise-induced nonsustained VT—that rapidly degenerated into ventricular fibrillation, resulting in hemodynamic collapse and requiring external defibrillation. Given the high-risk phenotype and inducibility of sustained monomorphic VT progressing to ventricular fibrillation, transvenous implantable cardioverter-defibrillator (ICD) implantation for secondary prevention was prioritized over ablation.

Genetic analysis identified a heterozygous, likely pathogenic variant (c.916G>T, exon 10) in the *TECRL* gene, associated with catecholaminergic polymorphic ventricular tachycardia type 3 (CPVT3). While TECRL is classically associated with autosomal recessive CPVT3, recent evidence suggests that certain heterozygous *TECRL* variants may contribute to a CPVT-like phenotype, potentially through gene dosage-dependent mechanisms. Functional studies have shown altered intracellular calcium handling and abnormal action potential properties even in heterozygous models, supporting a possible contributory role of single-allele *TECRL* variants in arrhythmogenesis. Therefore, while the detected variant may not independently account for the phenotype, it may represent a modulatory substrate in combination with the structural scar-related substrate.

Considering TECRL genotype and arrhythmic phenotype, beta-blocker therapy was optimized by switching from bisoprolol to nonselective propranolol, given the higher efficacy of nonselective beta-blockers in CPVT3 and the current evidence favoring combination regimens in selected cases. Structured exercise restriction was also recommended. The opportunity for catheter ablation, as well as adjunctive therapies including the use of flecainide and left cardiac sympathetic denervation, was discussed with the patient. A shared decision was made to defer these options, to be reconsidered in the event of arrhythmic recurrences or ICD interventions.

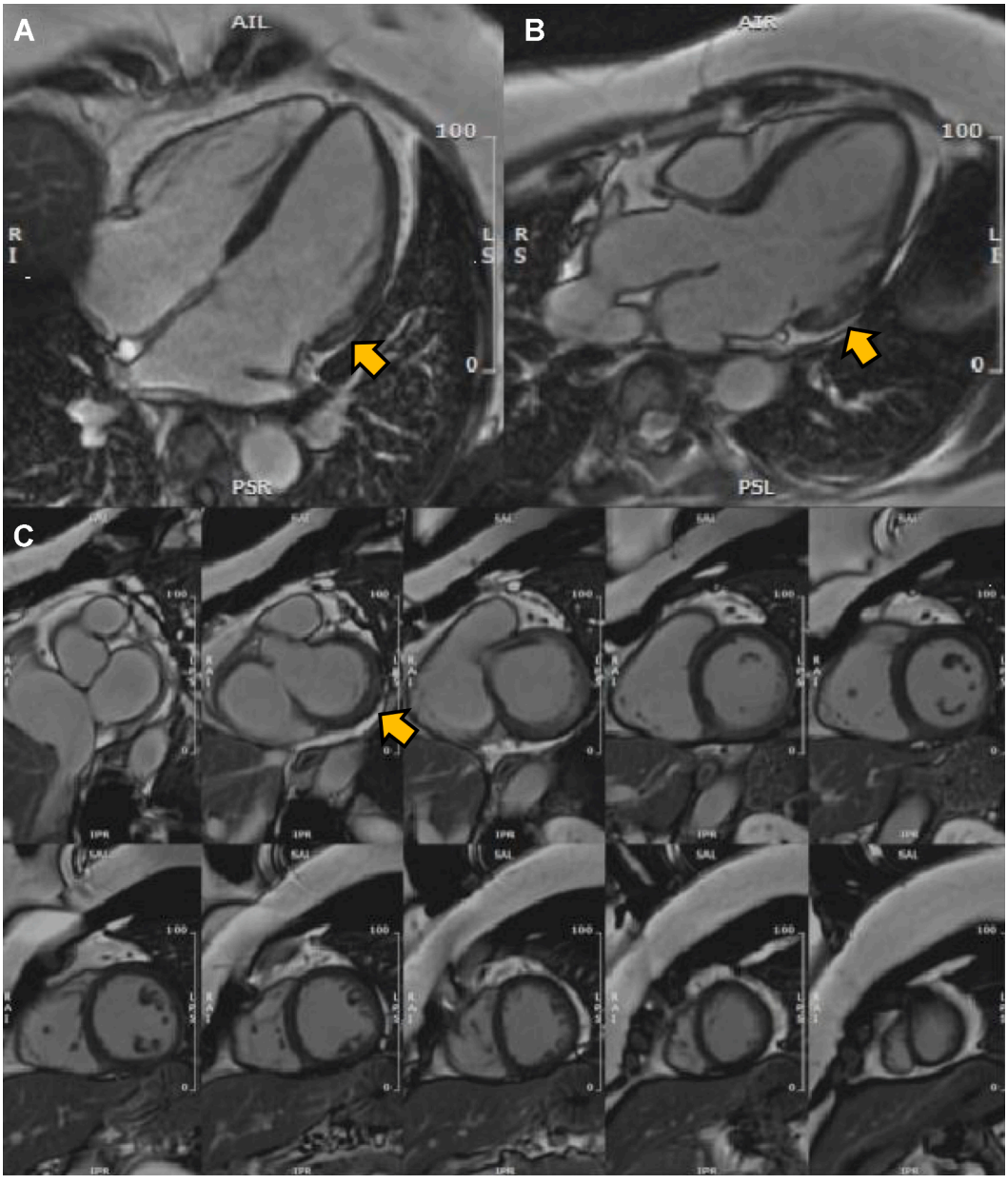
OUTCOME AND FOLLOW-UP

At the 12-month follow-up, the patient remained clinically stable and asymptomatic. ICD interrogations continued to show multiple episodes of self-terminating VT, without any need for antitachycardia pacing or shock delivery. Propranolol therapy was maintained without modification. Genetic counseling was reiterated during follow-up. Although TECRL-associated CPVT3 follows an autosomal recessive inheritance pattern, the potential modulatory role of heterozygous variants was discussed in light of recent evidence. Cascade genetic screening remained recommended to clarify inheritance patterns and reproductive risk. However, both the patient's daughter and the father of the child opted to defer genetic testing, reserving the decision for future consideration.

DISCUSSION

This case exemplifies a dual arrhythmic phenotype underlying a complex clinical presentation, with

FIGURE 3 Cardiac Magnetic Resonance Showing Scar Imaging



Postcontrast PSIR sequences: (A) 4-chamber view, (B) 3-chamber view, and (C) short-axis view demonstrate late gadolinium enhancement of the midbasal inferior and lateral walls of the left ventricle (yellow arrows). PSIR = phase-sensitive inversion-recovery.

scar-mediated monomorphic VT sustained by a protected conduction channel, and a concurrent catecholaminergic mechanism suggested by polymorphic PVCs, exercise-induced arrhythmias, and rapid degeneration to ventricular fibrillation—hallmarks of CPVT. Although bidirectional VT is classically described in CPVT, it is seen in less than one-half of the cases, and many patients present with polymorphic PVCs and nonsustained VT that can progress to ventricular fibrillation under adrenergic stress.[2]

Myocardial scar represents a key arrhythmogenic substrate, particularly through macro-re-entrant mechanisms. Scar-related VT is typically sustained by a slow-conducting channel of border zone tissue,

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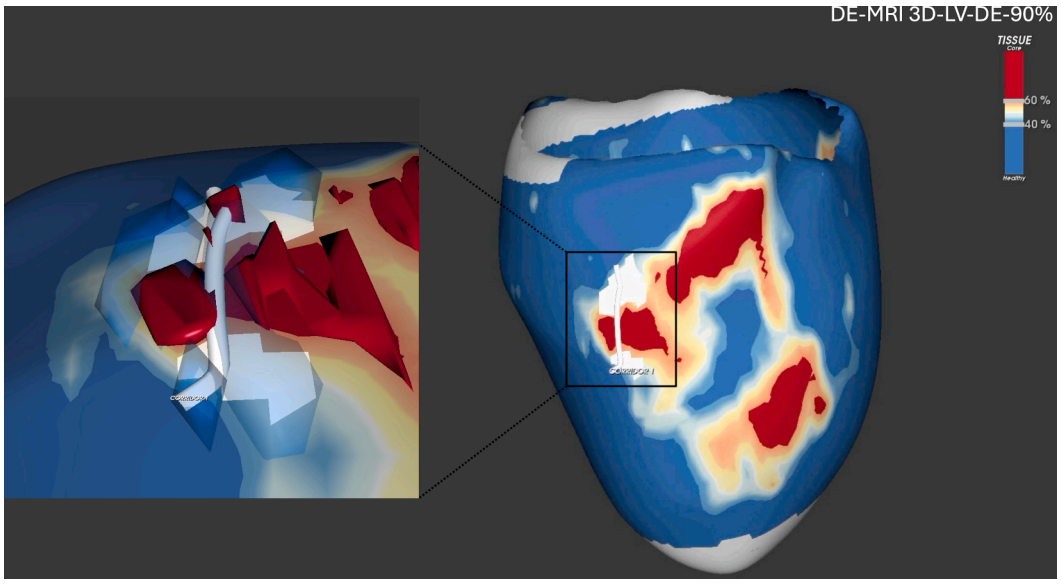
FIGURE 4 **Cardiac Magnetic Resonance Showing Substrate Imaging With Conduction Channel Mapping**



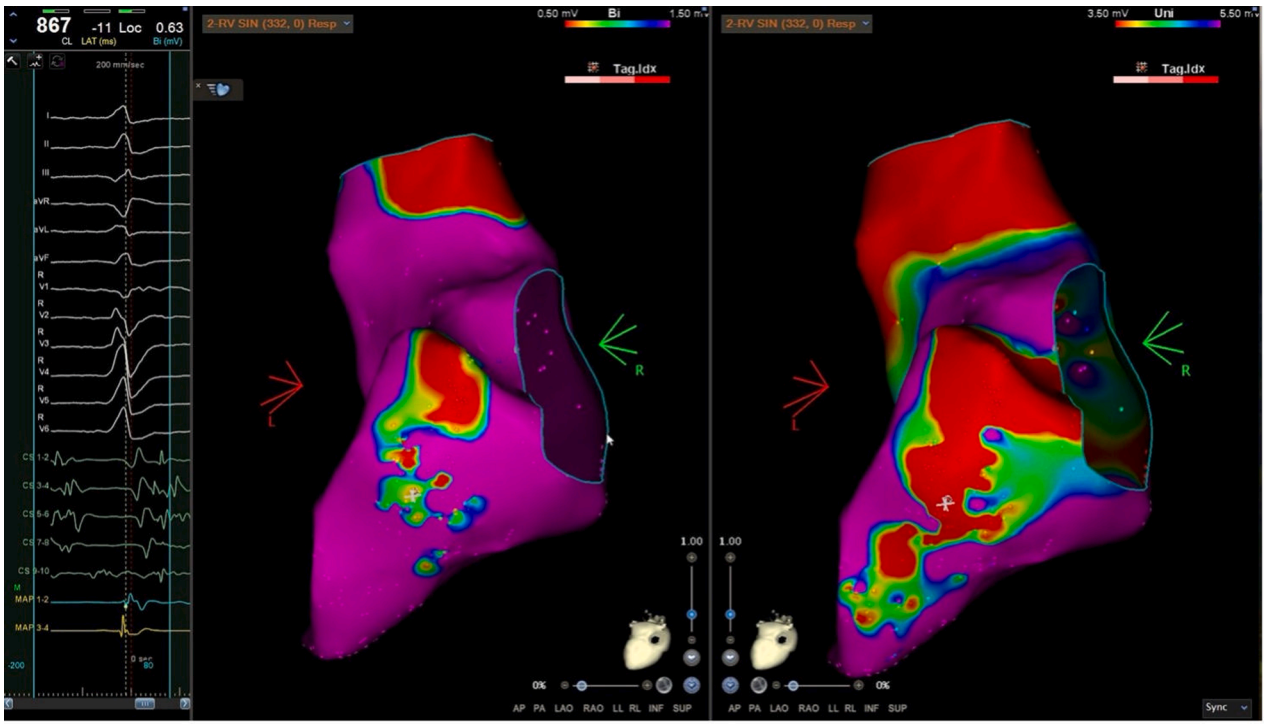
Three-dimensional shell of the subepicardial layer (90% of left ventricular wall thickness) demonstrating a nonischemic scar involving the midbasal inferior and lateral walls of the left ventricle, characterized by a dense core and surrounding heterogeneous tissue. A putative conduction corridor with medium protectedness is visualized, representing an anatomical substrate for re-entrant ventricular arrhythmia.

insulated by dense scar and connecting 2 regions of excitable myocardium. This structural configuration enables re-entrant circuits and underlies many clinical VT presentations. In this patient, frequent PVCs and nonsustained VT were documented, with initiation consistently triggered by a PVC of different morphology from the predominant ectopic pattern. This observation supports a trigger-substrate interaction. Advanced CMR imaging enabled precise identification of a nonischemic scar—possibly secondary to a prior inflammatory process or a gene-elusive cardiomyopathy—localized to the midbasal inferolateral wall and, critically, a putative conduction corridor within the border zone region. The corridor exhibited medium protectedness and corresponded anatomically to the critical isthmus identified during electrophysiological study. This alignment confirms the value of high-resolution scar imaging and pixel signal intensity analysis defining functional arrhythmogenic circuits.

Although the presence of LGE on CMR has been associated with increased risk of VT and sudden cardiac death in diverse patient populations, not all scars confer equivalent arrhythmic potential. Several studies have emphasized that scar heterogeneity and channel architecture—rather than total scar burden—are stronger predictors of arrhythmogenesis. Three-dimensional LGE imaging and scar architecture analysis allow for detailed scar segmentation, enabling identification of putative conduction corridors based on core/border zone distribution. Parameters such as channel mass, length, transmurality, and protectedness, assessed via dedicated post-processing software, have been proposed as key metrics to inform procedural planning and risk stratification.[3,4] It has been emphasized that conduction channel architecture assessed by 3D LGE imaging may correlate with the most probable re-entrant circuits and guide tailored ablation strategies.[5] Other studies have reinforced the role of 3D CMR in identifying conduction channels and improving VT substrate delineation. Therefore, integration of structural imaging with electroanatomic mapping is increasingly recognized as a cornerstone in the management of scar-related VT.[6]

Genetic predisposition may further contribute to arrhythmogenic susceptibility, and it interacts with structural substrates to modulate risk. In our case, genetic testing identified a heterozygous, likely pathogenic variant in the *TECRL* gene, associated with CPVT3. TECRL plays a role in fatty acid metabolism and intracellular calcium regulation, and biallelic pathogenic variants are associated with adrenergically mediated polymorphic VT in the

FIGURE 5 **Electroanatomic Mapping**



Electroanatomic mapping confirmed low-voltage areas localized to the basal inferior wall with significant epicardial extension. A critical isthmus was identified within these areas, consistent with the putative corridor identified by the cardiac magnetic resonance study.

absence of structural abnormalities.[7] Although CPVT3 is classically inherited in an autosomal recessive manner, emerging data suggest that heterozygous *TECRL* variants may exert a proarrhythmic effect in selected cases, possibly through gene dosage-dependent mechanisms,[8] raising the hypothesis that such variants may act as susceptibility modifiers, even in structurally abnormal hearts.

Our case supports the concept of a composite arrhythmogenic mechanism, in which myocardial scar and a structurally protected conduction channel represent the substrate for re-entry, while the heterozygous *TECRL* variant may contribute to the overall arrhythmic phenotype by modulating ectopic activity and electrical instability. This reinforces the need for an integrated diagnostic approach that combines imaging, electrophysiological evaluation, and genetic profiling to capture the multifactorial nature of arrhythmogenesis.[9] Notably, in our case all diagnostic assessments, including exercise testing and programmed ventricular stimulation, were conducted while the patient was receiving bisoprolol, a cardioselective beta-blocker with limited efficacy in catecholaminergic or CPVT-like phenotypes. After ICD implantation and genetic testing, therapy was optimized by switching to propranolol. Although nadolol is currently considered the preferred option based on clinical evidence and consensus recommendations, it was temporarily unavailable at the time of the evaluation because of a national supply shortage. In line with the 2022 European Society of Cardiology guidelines[9] and the 2021 Pediatric and Congenital Electrophysiology Society Consensus Statement,[10] additional therapeutic strategies—including sympathetic denervation and flecainide—were discussed with the patient and retained as individualized, deferred strategies to be reconsidered in the event of arrhythmic recurrences or appropriate ICD therapies.

CONCLUSIONS

This case highlights the clinical utility of advanced CMR imaging in defining scar architecture and detecting conduction corridors that may serve as anatomical substrates for VT. The integration of advanced substrate imaging, electroanatomic mapping, and genetic analysis enabled comprehensive

characterization of the arrhythmic mechanism. Importantly, this case illustrates a dual arrhythmogenic mechanism integrating scar-mediated re-entry shaped by protected channelized architecture and genetically modulated electrical instability. The integration of imaging, electrophysiology, and molecular genetics represents a contemporary *imagenomic* model for arrhythmic risk stratification and individualized clinical management.

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KEY WORDS cardiac magnetic resonance, conducting channels, inherited arrhythmia syndromes, scar, ventricular arrhythmias

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