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EDITOR'S PAGE


The Hidden Scars of Arrhythmogenic (Right Ventricular) Cardiomyopathy

Silent Substrates for Ventricular Arrhythmias

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In the ever-expanding world of cardiomyopathies, the once-simple classification is increasingly transformed into a complex landscape with a diverse array of genetic forms of disease.[1] This growing recognition of distinct cardiomyopathies challenges us to refine our understanding continuously, to remain open to new developments, and to see each patient not as a mere diagnosis but as a unique expression of an intricate genetic disease. Among these entities, arrhythmogenic cardiomyopathy (ACM) holds a special place, its threads of inheritance linked with the spectrum of structural and functional abnormalities and ventricular arrhythmias that often lead to sudden cardiac death at a young age.[2-4] ACM and its well-known subtype, arrhythmogenic right ventricular cardiomyopathy (ARVC), draw attention to the distinct natural history of disease in specific genetic forms. ARVC predominantly affects the right ventricle (RV), although the left ventricle is increasingly considered to be involved in at least one-half of the cases.[5] The diagnosis of ARVC is based on a combination of major and minor Task Force Criteria (TFC), which include functional, structural, electrocardiographic, arrhythmic, pathological, and genetic/family history information.[6] The true nature of ARVC lies in its unpredictability—the ever-present prospect that ventricular arrhythmia may be the sentinel (and final) sign of disease, particularly in probands with pathogenic/likely pathogenic *PKP2* variants.

ARVC is typically caused by heterozygous pathogenic/likely pathogenic variants in desmosomal genes and follows an autosomal dominant inheritance pattern, with male sex and endurance exercise associated with a significantly higher risk of ventricular arrhythmias.[7] In many cases, recognizing ARVC is appreciating a pattern that runs through families. Yet, awareness of the variable presentations of this disease remains limited within the cardiology community. Perhaps its rarity obscures its presence, or maybe the phenotypic overlap with other inherited and inflammatory cardiomyopathies makes timely diagnosis challenging.[8,9] Moreover, the variable expressivity of disease leads to a significant proportion of cases mislabeled as idiopathic ventricular tachycardia (VT), which may eventually lead to underestimation of risk in this high-risk population, denying the potentially life-saving secondary preventive implantable cardioverter-defibrillator implantation.[10]

Consider the case of a young man, age 33 years, who was referred to our center following an encounter at an outside hospital. At the presentation to the emergency department, his only symptom was palpitations; his heart rate was found to be at 185 beats/min, and his blood pressure was in a normal range. His electrocardiogram (ECG) showed a wide complex tachycardia (**Figure 1**). After initiation of intravenous amiodarone, he developed symptomatic hypotension, and cardioversion was performed to restore sinus rhythm (**Figure 2**). He had no history of

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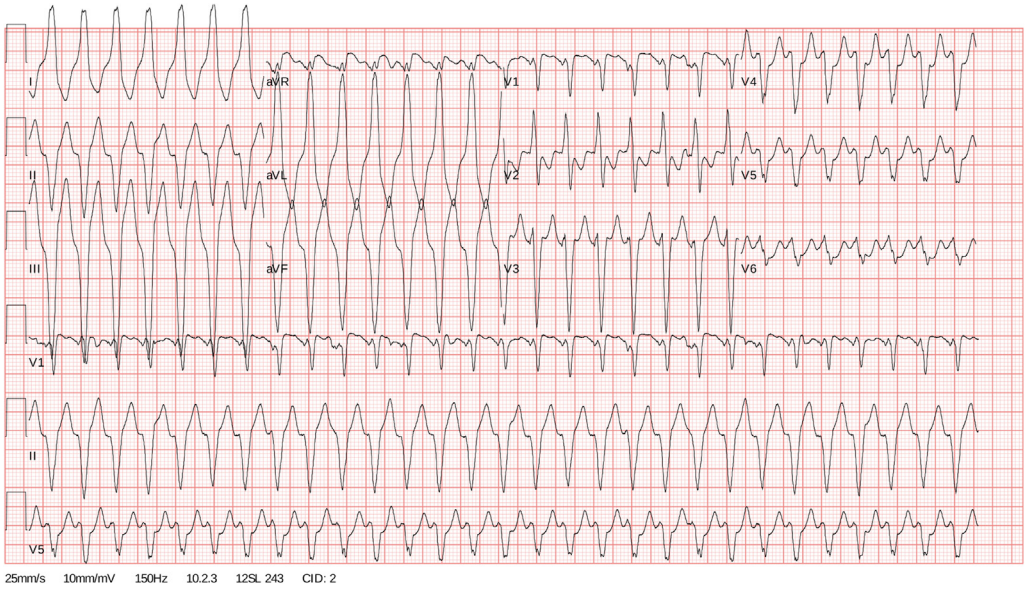
FIGURE 1 ECG of the Wide Complex Tachycardia Recorded at Presentation to the Emergency Department



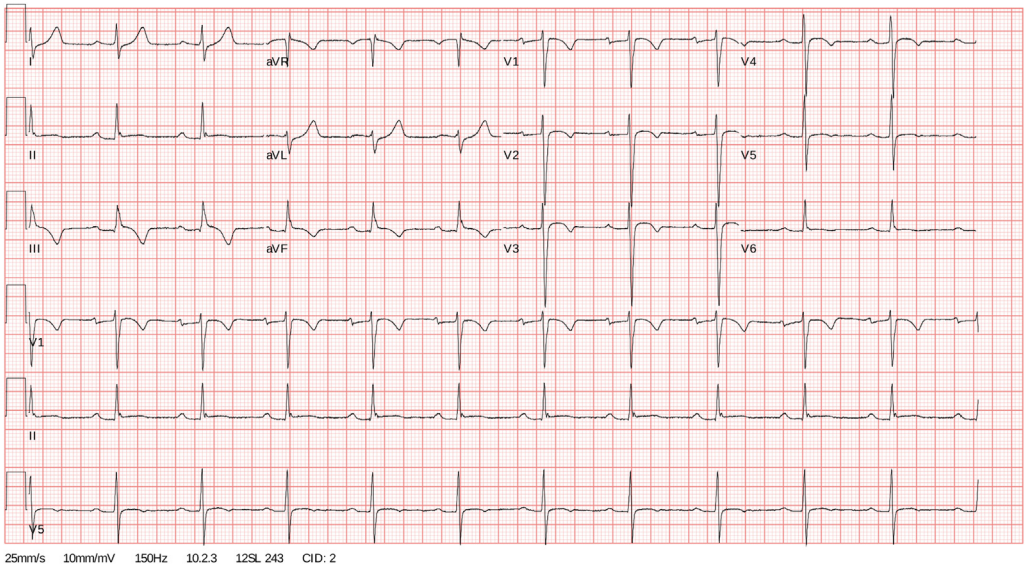
prior syncopal episodes. Normal coronary angiography, echocardiogram, and cardiac magnetic resonance imaging left more questions than answers, leading him to our clinic for further evaluation.

It was in the careful examination of his ECG that the story of ARVC began to unfold. The wide complex tachycardia displayed a left bundle branch block-like morphology, with a superior axis and, remarkably, AV dissociation, diagnostic for VT. His ECG obtained later during the hospital course showed T-wave inversions (TWI) in precordial (V_1-V_4) and inferior leads (III and aVF), the former fulfilling a major diagnostic criterion for ARVC per the 2010 TFC.[6] His family history, too, was remarkable: 2 maternal uncles were lost to sudden death in their 40s to 50s, their stories now reinterpreted through the lens of possible heritable risk.

Further evaluation through an electrophysiological study provided deeper insights into the arrhythmogenic substrate, solidifying the diagnosis (**Figure 3**). The RV endocardial burst pacing induced the clinical VT, with a cycle length of 322 ms, exhibiting the hallmark characteristics of ARVC-associated VT: a left bundle branch block-like morphology with a superior axis. Yet, as is often the case in ARVC, the clinical lessons go further. Endocardial ablation of the VT did not terminate it; thus, epicardial 3D electroanatomic mapping was performed, revealing significant low-voltage areas across the epicardial surface of the RV. These areas of scarred myocardium create the substrate for re-entrant circuits, where abnormal electrical impulses can propagate, sustaining VT. This discrepancy between imaging and electrical substrate emphasizes a crucial aspect of ARVC: electrophysiological features—as also demonstrated by precordial and inferior lead TWI on 12-lead ECG and presentation with sustained VT—often precede morphofunctional abnormalities detectable through conventional imaging in patients with typical ARVC.[2]

During the procedure, both endocardial and epicardial ablation were performed, targeting these critical scar regions (**Figure 4**). Although epicardial ablation was successful in terminating the clinical VT (Video 1), the induction of multiple other VT morphologies reflected the presence of an extensive arrhythmia substrate. Such complexity also reinforces the need for timely secondary preventive implantable cardioverter-defibrillator implantation as an essential safeguard against sudden cardiac death, which we pursued in our patient. In this context, while catheter ablation may help effectively reduce the burden of future VT events and thereby the likelihood of appropriate device interventions,[11] it does not alter the disease's progressive nature.[10]

FIGURE 2 **Resting ECG Recorded During the Hospitalization**

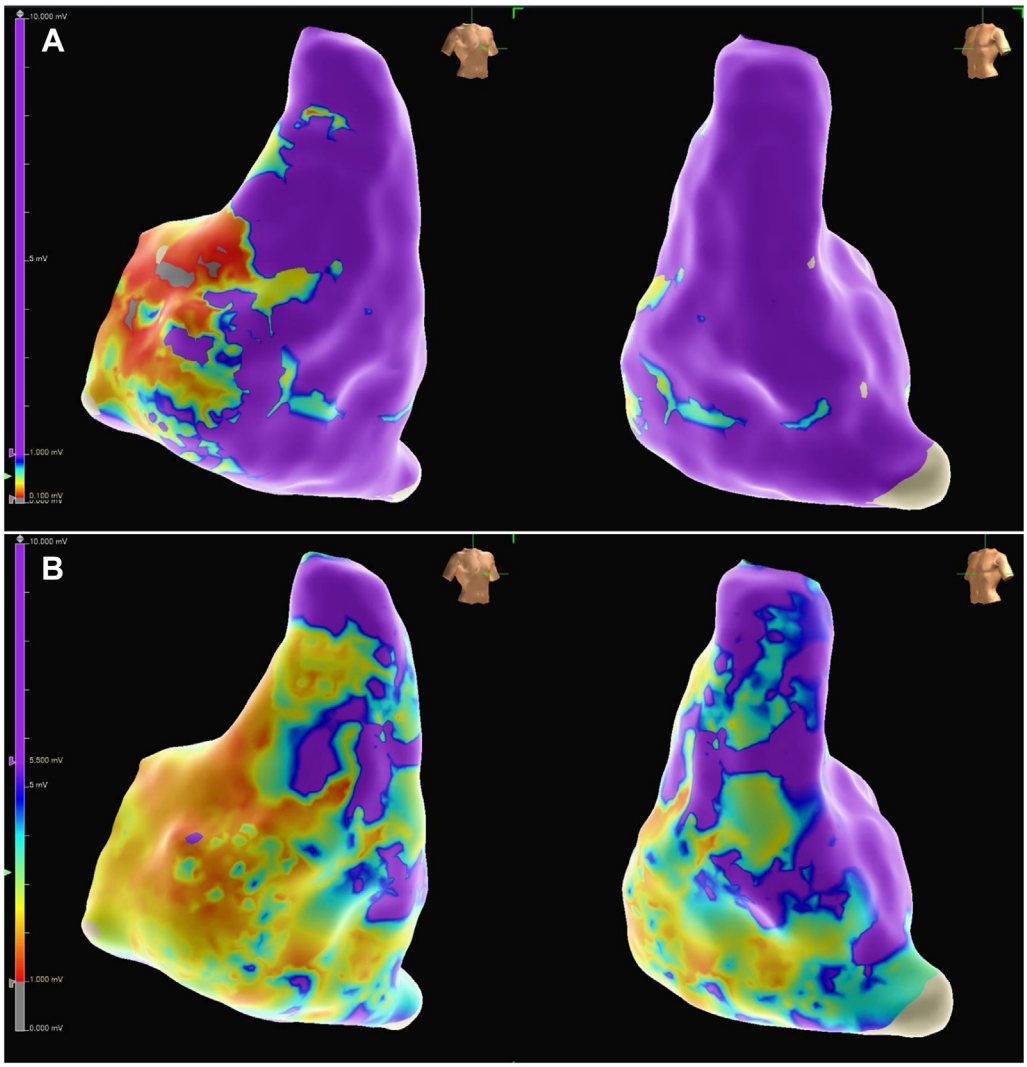


The patient's family history offered additional insight; the death of 2 uncles in their 40s to 50s (although without autopsy) serves as a critical reminder that family history, even when not meeting specific TFC, can be an invaluable guide in ARVC. Indeed, genetic testing revealed a splice donor heterozygous likely pathogenic variant c.336+1G>A in the *PKP2* gene, supporting the diagnosis of ARVC and further supporting cascade screening for relatives at potential risk.

In our case, although the patient's initial imaging work-up at an outside hospital showed no overt abnormalities, he met the 2010 TFC for ARVC based on the sustained VT and precordial TWI, both major criteria for ARVC diagnosis.[6] He subsequently had genetic testing, which revealed a likely pathogenic *PKP2* variant—adding another major criterion to his 2010 TFC. The discovery of multiple VT morphologies, the extensive scarring, and the family history underscore that the absence of morphofunctional abnormalities on imaging does not negate the underlying arrhythmic risk, particularly in *PKP2*-related ARVC. This fact must guide the ongoing proactive management of these patients.

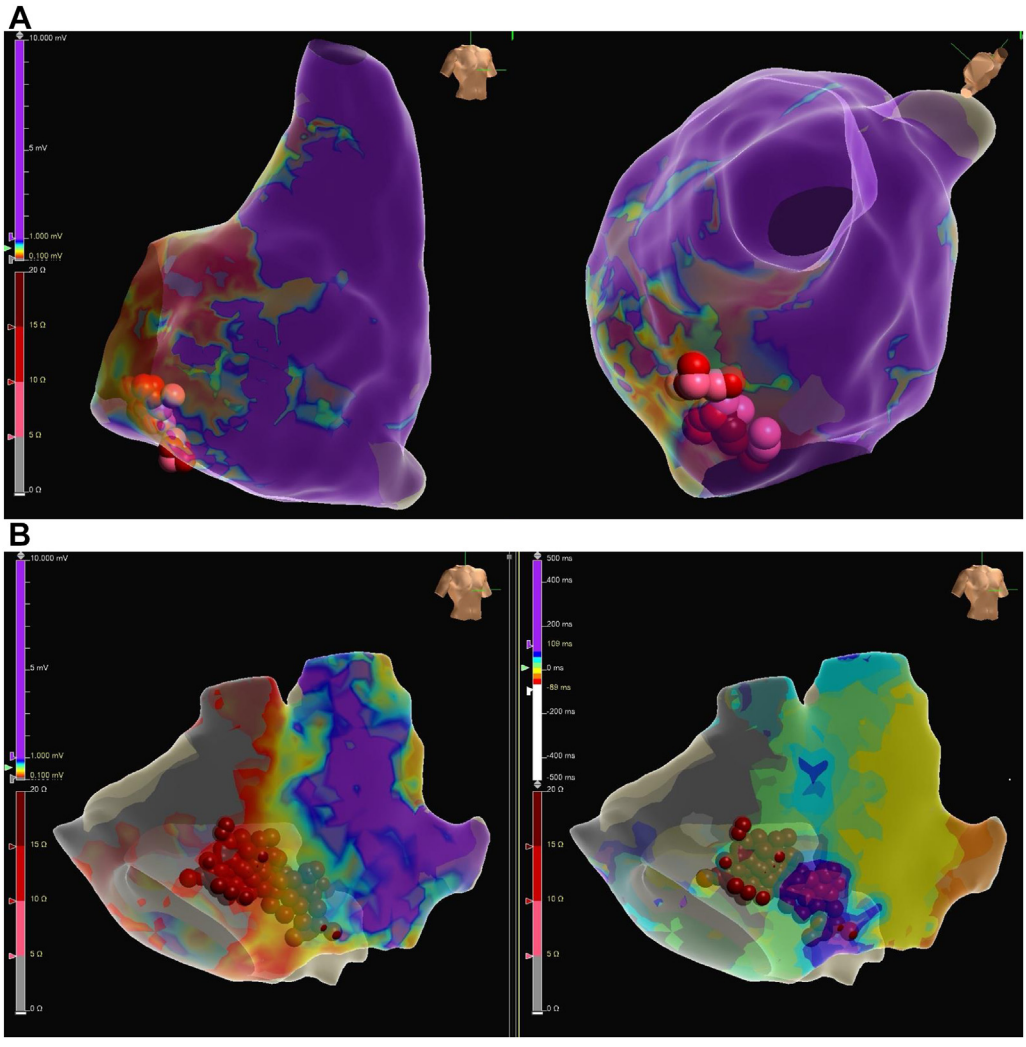
As we learn more about genotype-phenotype correlations within ACM,[1,12,13] the picture becomes richer, more nuanced, and more personalized. The challenge is not only to manage the disease, but also to anticipate its trajectory, to prepare families, and to protect future generations from the same fate. Each diagnosis is both a challenge and a lesson—an opportunity to see beyond the present moment, to consider the past, and to act with foresight for the future.

FIGURE 3 Endocardial Omnipolar and Unipolar 3-Dimensional Electroanatomical Voltage Maps of the Right Ventricle Obtained in Sinus Rhythm



(A) Right anterior oblique (left panel) and left anterior oblique (right panel) views of endocardial omnipolar 3-dimensional electroanatomical voltage map of the right ventricle obtained in sinus rhythm (0.1-1 mV), demonstrating low-voltage areas (nonpurple regions). The omnipolar technology is a novel mapping tool used to acquire omnipolar signals by integrating signals of 3 adjacent electrodes (a clique of 3) that are organized in a triangular pattern. Using the HD Grid mapping catheter, omnipolar maps display a higher resolution compared with standard bipole and HD wave maps. (B) Right anterior oblique (left panel) and left anterior oblique (right panel) views of endocardial unipolar 3-dimensional electroanatomical voltage map of the right ventricle obtained in sinus rhythm (1-5.5 mV), demonstrating extensive low-voltage areas. A combination of low unipolar and low omnipolar voltage is more indicative of true low-voltage areas.

FIGURE 4 **Endocardial and Epicardial 3-Dimensional Electroanatomical Maps of the Right Ventricle Obtained in Sinus Rhythm With Demonstration of Ablation Sites**



(A) Right anterior oblique (left panel) and right anterior oblique caudal (right panel) views of right ventricular endocardial omnipolar 3-dimensional electroanatomical voltage map obtained in sinus rhythm (0.1-1 mV), with demonstration of endocardial ablation sites (red dots). (B) Right ventricular epicardial 3-dimensional electroanatomical voltage (left panel) and isochronal late activation maps (right panel) during sinus rhythm with demonstration of epicardial ablation sites (red dots).

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REFERENCES

1. Gasperetti A, Asatryan B. Disputation on the power and efficacy of phenotypical classification in arrhythmogenic cardiomyopathy: time for a reformation?!. *Heart Rhythm*. 2024;21:679-681.

2. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2017;136:2068-2082.

3. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44:3503-3626.

4. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med*. 2017;376:1489-1490.

5. Zghaib T, Te Riele A, James CA, et al. Left ventricular fibro-fatty replacement in arrhythmogenic right ventricular dysplasia/cardiomyopathy: prevalence, patterns, and association with arrhythmias. *J Cardiovasc Magn Reson*. 2021;23:58.

6. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533-1541.

7. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol*. 2013;62:1290-1297.

8. Gasperetti A, Rossi VA, Chiodini A, et al. Differentiating hereditary arrhythmogenic right ventricular cardiomyopathy from cardiac sarcoidosis fulfilling 2010 ARVC Task Force Criteria. *Heart Rhythm*. 2021;18:231-238.

9. Sampognaro JR, Gaine SP, Sharma A, et al. Diagnostic pitfalls in patients referred for arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm*. 2023;20:1720-1726.

10. Wang W, Cadrin-Tourigny J, Bhonsale A, et al. Arrhythmic outcome of arrhythmogenic right ventricular cardiomyopathy patients without implantable defibrillators. *J Cardiovasc Electrophysiol*. 2018;29:1396-1402.

11. Gasperetti A, Peretto G, Muller SA, et al. Catheter ablation for ventricular tachycardia in patients with desmoplakin cardiomyopathy. *JACC Clin Electrophysiol*. 2024;10:487-498.

12. Protonotarios A, Bariani R, Cappelletto C, et al. Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator. *Eur Heart J*. 2022;43:3053-3067.

13. Carrick RT, Gasperetti A, Protonotarios A, et al. A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers. *Eur Heart J*. 2024;45:2968-2979.

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