9 Right Ventricular Dysfunction and Ventricular Arrhythmias: Challenges in Diagnosis

Wendy S. Tzou

9.1 Case Summary

A 37 man presents for routine follow-up with history of sustained palpitations 15 years ago, but no recurrent episodes since. His baseline 12-lead ECG was abnormal (Fig. 9.1a–c). On subsequent work-up, transthoracic echocardiography demonstrated normal left ventricular (LV) size and systolic function and borderline dilated right ventricle (RV) with mild systolic dysfunction, most pronounced in the mid and apical segments. He was noninducible for sustained arrhythmias on electrophysiological study. However, he did have frequent, multifocal premature ventricular contractions (PVCs) and nonsustained ventricular tachycardia (NSVT), of both right-bundle and left-bundle morphologies, on isoproterenol challenge as well as during stress testing, as well as frequent (15%) multifocal PVCs on Holter monitoring (Fig. 9.1a–c). Cardiac magnetic resonance imaging (Video 9.1) showed focal regions of dyskinesis involving the basal RV free wall extending to the RV outflow tract. RV size was normal (end-diastolic volume normalized for body-surface area = 81 mL/m^2) but RV ejection fraction (EF) was reduced (39%). There was a small region of late gadolinium enhancement, but involving only the biventricular apex and apical portion of the interventricular septum. Genetic testing was negative. What is his presumed diagnosis, and what can be done to further clarify the diagnosis?

9.2 Case Discussion

He meets a clinical diagnosis of "definite" arrhythmogenic right ventricular cardiomyopathy (ARVC) based on the presence of two major criteria (regional RV dyskinesia and RVEF ≤40% + inverted T waves in right precordial leads or beyond in absence of complete right bundle branch block), as well as one minor criterion (>500 PVCs in 24 h on Holter), based on 2010 Revised Task Force Criteria [1]. However, his family history is notable for longevity (all grandparents lived into their 90s, both of his parents, who are in their 70s, are alive and well, and adult siblings similarly are alive and well). Other than the episode of palpitations more than a decade ago, he has not had recurrent symptoms, even with relatively high PVC burden. He does not yet have an implantable cardioverter-defibrillator (ICD).

There are multiple arrhythmogenic cardiomyopathies that can affect primarily the RV that are not due to ARVC, and may, in fact, have different prognoses as well as associated treatments. Increasingly recognized entities include cardiac sarcoidosis, myocarditis, and even exercise-induced arrhythmogenic remodeling [2]. All of these etiologies can produce RV dysfunction and even substrate for ventricular arrhythmias. A feature that distinguishes ARVC from the others is that it is an inherited disorder resulting from a variety of desmosomal or non-desmosomal gene mutations. Although it is classically inherited in autosomal dominant fashion, penetrance is incomplete, phenotypic expression can be variable, and de novo mutations may lead to sporadic cases. In the latter cases in particular, standard diagnosis based on noninvasive criteria can be particularly limited in accuracy, including genetic testing [3]. Furthermore, significant anxiety may accompany the diagnosis due to the implications for first degree relatives, and, especially, for offspring, for whom routine, subsequent screening (and treatment if appropriate) also is recommended [4]. Treatments in ARVC are typically geared toward treatment or prevention of ventricular arrhythmias, which often includes ICD implantation in high-risk individuals, and can include therapies tailored toward

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-28533-3_9) contains supplementary material, which is available to authorized users.

W. S. Tzou (✉)
Division of Cardiology, Cardiac Electrophysiology Section, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: wendy.tzou@ucdenver.edu

A. Natale et al. (eds.), *Cardiac Electrophysiology*, https://doi.org/10.1007/978-3-030-28533-3_9

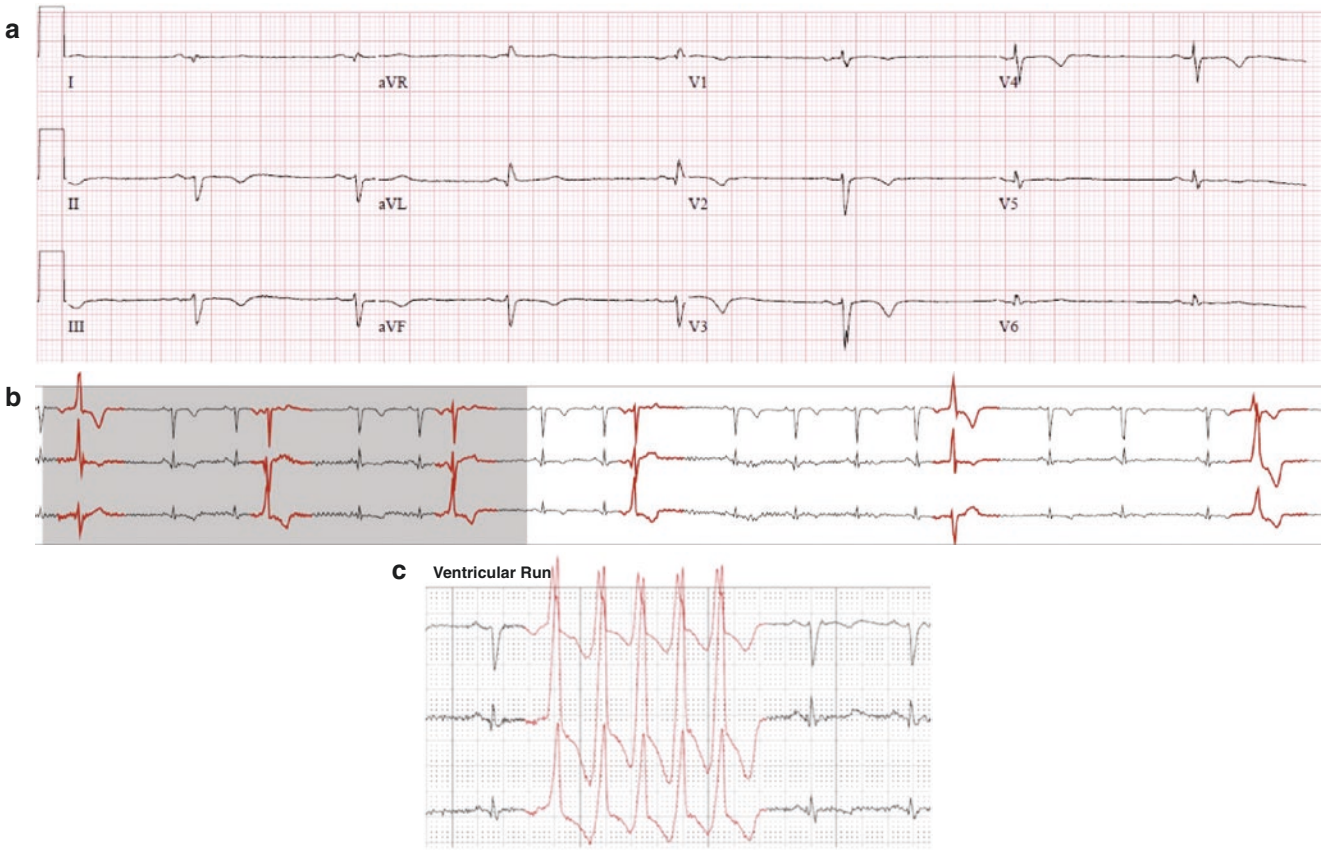

Fig. 9.1 (**a**) Baseline 12-lead ECG. (**b**) Multifocal premature ventricular complexes (PVCs) observed on Holter monitoring. (**c**) Non-sustained ventricular tachycardia of different exit compared to the isolated PVCs

mitigation of RV dysfunction and failure, including exercise restrictions for those previously participating in endurance or competitive sports [4].

The overall sensitivity for conventional endomyocardial biopsy (EMB) in diagnosing ARVC is generally low, primarily due to the fact that EMB samples are typically acquired from the interventricular septum, given relative safety compared to sampling from the RV free wall, but the interventricular septum is usually not affected in ARVC. A strategy of voltage-map-guided EMB using conventional electroanatomic mapping (EAM) has demonstrated high sensitivity and yield, not only for diagnosis of ARVC, but also in diagnosis of the other disease entities noted above that may mimic ARVC, including myocarditis [3]. In one previous series demonstrating the potential utility of EAM-guided EMB, nearly 50% of definite ARVC patients were found to actually have active myocarditis [3].

Based on this information and persisting diagnostic uncertainty, the present patient underwent EAM-guided EMB. Using the Precision EAM system (Abbott, Minneapolis, MN), a high-density voltage map was created, which demonstrated grossly normal endocardial RV bipolar voltage and electrograms, except for a very small area on the mid-RV septum, which contained low-amplitude and fractionated signals (Fig. 9.2). Electrophysiological study was performed, during which ventricular fibrillation (VF), but no ventricular tachycardia, was induced with tightly coupled triple ventricular extrastimuli. Two important points: (1) the yield of conventional EMB in this circumstance could have been very low given the grossly normal appearing regions everywhere else on the septum, and (2) the absence of bipolar abnormality anywhere but on this very focal aspect of the mid-interventricular septum is very unusual for ARVC. The bioptome utilized was able to be visualized within the EAM (Video 9.2) and then guided to the site of greatest interest, where 3 EMB samples were acquired.

The diagnosis from the samples obtained was consistent with patchy fibrosis and focal chronic inflammation involving ~50% of the tissue submitted, consistent with fibrotic scar secondary to remote myocardial damage (i.e. ischemia). The electron microscopic analysis also demonstrated absence of ultrastructural myocardial abnormality, inconsistent with ARVC. This case highlights limitations inherent in the widely utilized diagnostic criteria for ARVC and demonstrates the incremental value in EAM-guided EMB in selected patients to guide further treatment and prognosis.

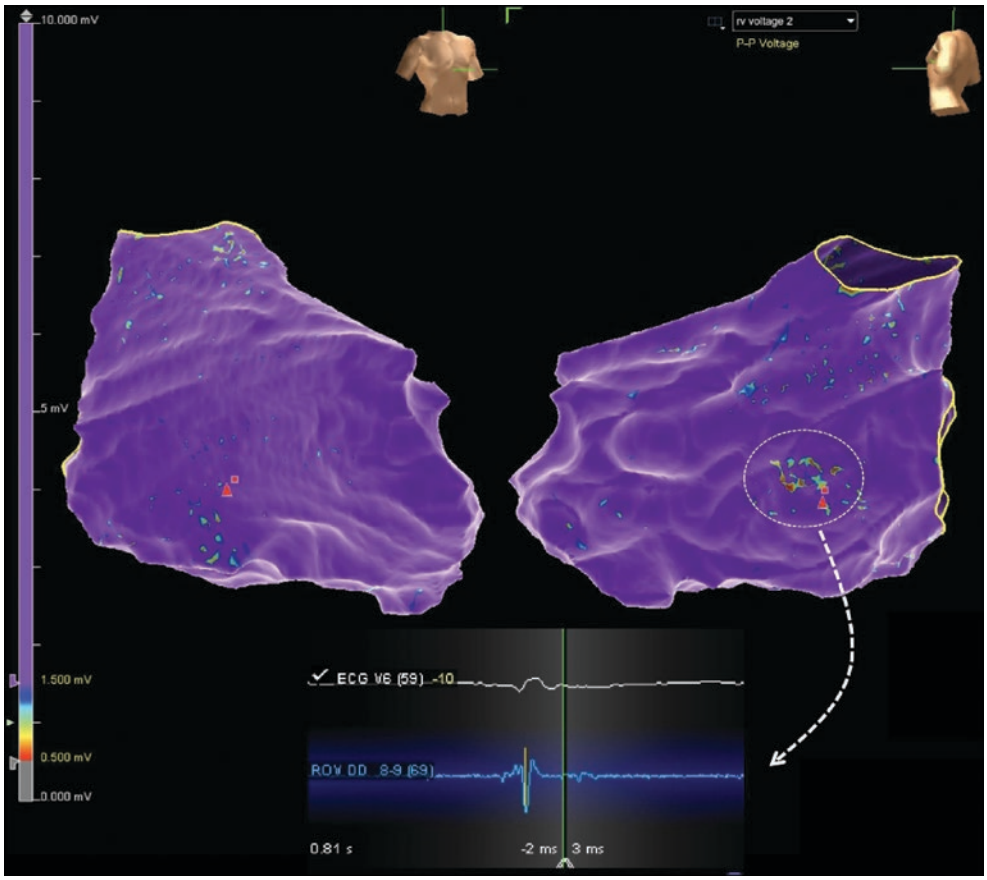

Fig. 9.2 Endocardial right ventricular bipolar voltage maps in right and left anterior oblique projections. Low-amplitude, fractionated signals with late potentials (inset, dotted arrow) present within the region of bipolar voltage <1.5 mV (dotted circle) confirm abnormality of the tissue with patchy-appearing low voltage

Also important in this case is that a final diagnosis remains unclear. Inducibility of any ventricular arrhythmia, including VF, has been associated with increased risk of subsequent ventricular arrhythmia events in patients who meet definite or even borderline criteria for a diagnosis of ARVC [5]. Given ARVC-like RV phenotype, mild exercise restrictions (no endurance or competitive sports) have been recommended, and ICD implantation has been discussed although deferred for now in the absence of ongoing symptoms.

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