Chapter 5
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

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Case Presentation

A 20-year-old man with history of cardiac arrest, status post implantable cardioverter defibrillator (ICD) presented for an evaluation after his ICD discharge. One year ago, he was shocked by the defibrillator and started on amiodarone 200 mg/day. On the day of presentation, two ICD shocks were delivered and he passed out. After regaining consciousness, he called emergency medical service and was brought to the emergency room. He reported no other symptoms at the time of initial evaluation. He had no family history of sudden cardiac death (SCD), premature coronary artery disease or familial cardiomyopathy.

Initial physical examination was notable for parasternal lift, grade 2/6 pansystolic murmur that was accentuated by inspiration on left lower sternal border, and the presence of palpable implanted device on left upper thorax. ECG shows sinus rhythm (Fig. 5.1) remarkable for right ventricular

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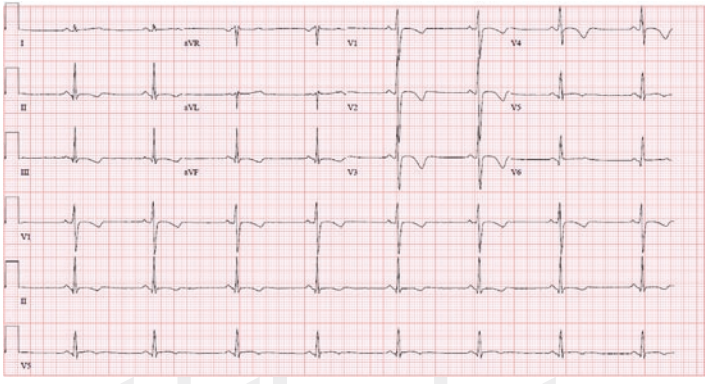

FIGURE 5.1 Sinus rhythm ECG. Note the T-wave inversions from V1 to V5, which are distinctly abnormal

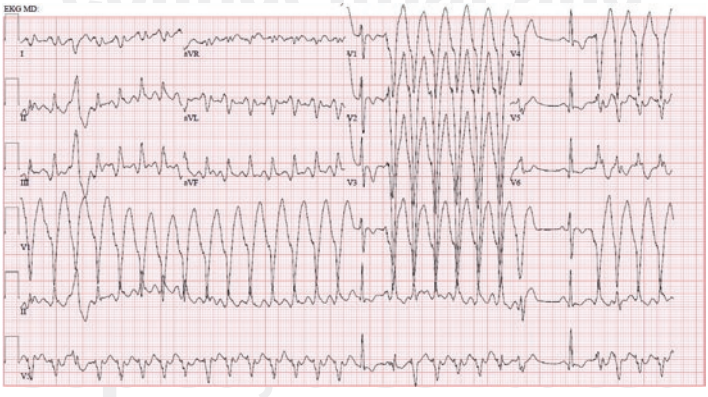

FIGURE 5.2 Wide complex tachycardia ECG. Note the left bundle branch block pattern which signifies that the arrhythmia is coming from the right ventricle

hypertrophy and T wave inversion in several leads (V1–V5, II, III, aVF). He was also noted to have intermittent non-sustained wide complex tachycardia (WCT) on telemetry, which was also captured by a 12-lead ECG (Fig. 5.2).

5.1 Our Initial Approach for Evaluation of this Patient

This patient presented with reported multiple ICD shocks associated with syncope. Thus, an ICD interrogation was indicated to confirm the presence of ICD shocks and to evaluate its cause. However, even before the interrogation, the presence of non-sustained WCT provided us an important clue of the underlying arrhythmia that may have caused the ICD shocks. The main differential of WCT includes ventricular tachycardia (VT), supraventricular tachycardia (SVT) with conduction delay, SVT with pre-excitation, and ventricular paced rhythm (Fig. 5.3).

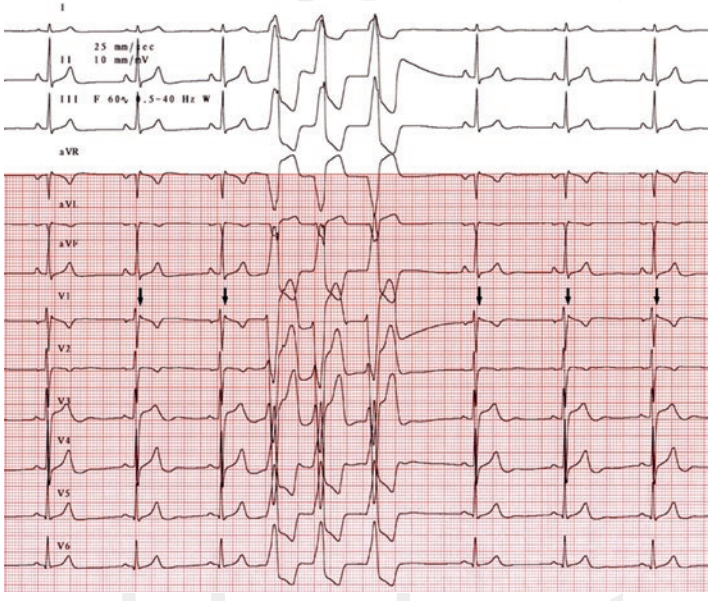

FIGURE 5.3 Epsilon waves. This 12-lead ECG from a *different* patient with ARVC demonstrates epsilon waves (arrow head). Also, 3-beat non-sustained VT with LBBB-like morphology/inferior axis is also demonstrated in the middle of the tracing

Given the history of heart disease, associated abnormal physical signs and ECG findings, as well as the presence of an ICD, the clinical likelihood that the WCT was a VT was already high. Although there were no ECG signs of atrioventricular dissociation (dissociated P wave, fusion beats, and captured beats), the QRS complex morphology during the tachycardia was more consistent with VT than SVT given (1) left bundle branch block (LBBB)-like QRS complex with RS > 70 ms in V2 and (2) initial r wave with duration >40 ms in aVR. Paced rhythm is highly unlikely at the rate of almost 180 beats/min as the upper tracking rate of the device is generally not programmed to exceed 150 beats/min. The subsequent ICD interrogation showed that the patient was shocked three times for a sudden onset, regular WCT with distinctly different QRS morphology from the recorded baseline. This was consistent with our suspicion of VT causing ICD shocks.

In patients with structural heart disease, VT with LBBB-like QRS morphology generally originates from right ventricle (RV) or interventricular septal myocardium. Various pathological processes can lead to the development of VT in these areas. However, in this patient with physical signs and electrocardiographic findings suggestive of predominant RV structural abnormalities, arrhythmogenic RV cardiomyopathy (ARVC) needs to be considered.

5.2 Terminologies: ARVC, ARVD, and ACM

ARVC, also termed arrhythmogenic right ventricular dysplasia (ARVD), is a genetic cardiomyopathy characterized by myocardial atrophy and fibrofatty replacement. This results in increased arrhythmogenicity and ventricular contractile dysfunction. The majority of ARVCs are caused by pathogenic mutations in genes encoding protein components of intercalated discs, such as desmosome [1]. Although ARVC was initially described as a disease of the (RV) [2], left ventricular involvement by the disease is not uncommon.

As the disease involvement is not limited to the RV, some authors use the term arrhythmogenic cardiomyopathy (ACM) instead of ARVC when referring to the disease. However, in the recent Heart Rhythm Society (HRS) expert consensus statement, this term is used more broadly to conceptualize a group of primary cardiomyopathies of various etiologies. This terminology excludes heart diseases due to coronary artery disease, hypertension, and valvular heart diseases that have arrhythmias as prominent presenting clinical features. Thus, ARVC represents one type of ACM [1]. To be consistent with this conceptual framework, the term ARVC will be used to refer to the disease in this article.

Also, some authors consider an ACM with predominant LV involvement a "variant" of ARVC. Although this might be true in some scenarios, in our opinion, there is insufficient evidence at this point to make a generalized conclusion. Thus, this article will focus on ARVC as diagnosed based on 2010 revised Task Force criteria.

5.3 What Is the Epidemiology and Pathophysiology of ARVC?

The prevalence of ARVC is not entirely clear and varies in different ethnic populations. The reported prevalence ranges from 0.6 to 1 case in 1000 persons [3, 4].

5.3.1 Pathology, Genetics, and Pathophysiology of ARVC

The pathological hallmark of ARVC is myocardial tissue atrophy and replacement by fibrofatty tissue [5–8]. The cardiomyocytes in the affected areas show degenerative features, apoptosis, and/or necrosis [7]. The degree of fibrosis in the affected tissue varies from minimal (*fatty variant*) to significant (*fibrofatty variant*) [5, 6, 8]. On electron microscopic

examination, intercalated disc structural abnormality and remodeling can be seen on the affected cardiomyocytes [9].

Intercalated discs are specialized structures on the cell membrane that connect adjacent cardiomyocytes and play vital roles in mechanical and electrical coupling as well as regulating cellular signaling pathways. They comprise of three main structures: desmosomes, fascia adherens, and gap junctions. The intercalated discs rely on orchestrated functions of these components [10].

In ARVC patients, pathogenic mutations in genes encoding components of the intercalated disc leads to qualitatively and/or quantitatively abnormal production of such proteins and, consequently, impaired functions of intercalated discs. Impaired mechanical coupling leads to cardiomyocyte detachment, death, and, in conjunction with abnormal cellular signaling, fibrofatty replacement [7, 11]. Impaired electrical coupling and fibrofatty tissue interposed between adjacent cardiomyocytes lead to slow, non-uniform electrical conduction, which predispose patients to the development of reentry arrhythmia [7, 11]. As the disease progresses, resulting in increased cardiomyocyte loss, ventricular wall motion abnormality, systolic dysfunction, and dilation ensue.

The pathogenic mutation of ARVC was first identified in junction plakoglobin (JUP) gene, encoding desmosomal proteins [12]. Subsequently, mutations were identified in other desmosomal genes, namely plakophilin-2 (PKP2), desmoglein-2 (DSG2), desmoplakin (DSP), and desmocollin-2 (DSC2). Overall, pathogenic desmosomal gene mutations were identified in approximately 50% of ARVC patients [13, 14]. Mutations in genes encoding non-desmosomal proteins have also been reported to cause ARVC but were identified in less than 10% of patients [13–15]. Most pathogenic mutations identified were heterozygous. Multiple mutations (homozygous, compound heterozygous, or digenic) were found in only approximately 6% of patients [7, 13, 16].

Given the incomplete penetrance and variable phenotypic expression of ARVC, environmental factors have been pro-

posed to play a role in its pathogenesis. Exercise has been associated with increased penetrance of ARVC in pathogenic desmosomal gene mutation carriers [17, 18]. Increased myocardial wall stress associated with exercise in conjunction with underlying impaired cardiomyocyte adhesion is hypothesized to accelerate cardiomyocyte detachment and death; thus, promoting the disease manifestation.

ARVC was initially thought to almost exclusively involve the RV, especially in the inflow, outflow, and apex, collectively called the "triangle of dysplasia" [2, 7]. However, LV involvement was found in 47% to 76% on pathological examination of the examined hearts (post-mortem or explanted) with ARVC [5, 8]. ARVC pathology generally progress from the subepicardial to subendocardial myocardium [7, 8].

5.4 What Are the Clinical Manifestations and Prognosis of ARVC?

ARVC patients usually present for clinical evaluation between the ages of 20–50 years with symptoms relating to ventricular arrhythmia (VA), such as palpitations, chest discomfort, presyncope, and syncope. Cardiac arrest and SCD can be the first presenting symptom in approximately 10% of patients [13, 19, 20]. VAs due to ARVC generally have LBBB-like morphology [20, 21], reflecting their RV origins, but can have superior or inferior axis [21]. VAs frequently recur during follow up and can lead to SCD [13, 19–21].

Most patients do not have heart failure symptoms early in the course of the disease [13, 20, 21]. As the disease progresses, symptoms of heart failure, especially right-sided (fatigue, exertional intolerance, lower extremity edema, and abdominal bloating), may subsequently develop from progressive contractile dysfunction and dilatation of the RV [13, 20]. Increasingly recognized is involvement of the LV, and dilation and subsequent left heart failure is seen as patients are not dying of arrhythmias. A small number of these patients require heart transplantation [13, 20].

ARVC is found to be familial in approximately 50–70% of patients [11, 13]; mainly inherited in an autosomal dominant pattern with incomplete penetrance and variable phenotypic expression [22, 23]. Autosomal recessive ARVC is rare and typically associated with characteristics cutaneous manifestation in the form of keratoderma striate on palmar and plantar surfaces as well as wooly hair [12, 24]. This constellation of abnormalities is named "Naxos syndrome" [24].

Overall, the prognosis of patients with ARVC in contemporary cohorts with utilization of ICD is reasonable [13, 19]. In a large cohort study of 439 ARVC patients with median follow up of 7 years, cardiac mortality and the need for cardiac transplantation occurred in 6% and 4% of patients, respectively [13]. SCD is the most important cause of death and is responsible for almost all deaths in patients without an ICD. In those with an ICD, deaths are more commonly due to heart failure and non-cardiac causes.

5.5 What Are the Diagnostic Tests Recommended for ARVC?

5.5.1 Electrocardiography (ECG)

Various ECG abnormalities reflect delayed/fragmented activation of the myocardium affected by ARVC. As ARVC predominantly involves the RV, these ECG abnormalities are most commonly observed in the right precordial leads (V1–V3) [25]. If they present on left precordial leads, LV involvement should be suspected [25]. Normal ECG can be seen in up to 12% of ARVC patients, especially in earlier stages [26]. ECG abnormalities are generally classified into depolarization and repolarization abnormalities [14].

Epsilon wave, prolonged terminal activation duration (TAD) of QRS complex, and late potentials on signal averaged ECG, are depolarization abnormalities that are relatively specific for ARVC. Thus, they are incorporated in the revised Task Force criteria for diagnosis of ARVC (see Table 5.1) [14, 25]. QRS fragmentation, incomplete and com-

TABLE 5.1 Revised task force criteria for diagnosis of ARVC

Criteria categories	Major criteria	Minor criteria
Global or regional dysfunction and structural alterations	• *By 2D echo* Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): – PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2) – PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥ 21 mm/m^2) – Or fractional area change ≤33% • *By MRI* Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: – Ratio of RV end-diastolic volume to BSA ≥ 110 mL/m^2 (male) or ≥ 100 mL/m^2 (female) – Or RV ejection fraction ≤40% • *By RV angiography* Regional RV akinesia, dyskinesia, or aneurysm	• *By 2D echo* Regional RV akinesia or dyskinesia and 1 of the following (end diastole): – PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥ 16 to <19 mm/m^2) – PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥ 18 to <21 mm/m^2) – Or fractional area change >33% to ≤40% • *By MRI* Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: – Ratio of RV end-diastolic volume to BSA ≥ 100 to <110 mL/m^2 (male) or ≥ 90 to <100 mL/m^2 (female) – Or RV ejection fraction >40% to ≤45%

(continued)

Table 5.1 (continued)

Criteria categories	Major criteria	Minor criteria
Tissue characterization of wall	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60–75% by morphometric analysis (or 50–65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	• Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥ 120 ms)	• Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 • Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block

Table 5.1 (continued)

Criteria categories	Major criteria	Minor criteria
Depolarization/ conduction abnormalities	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1–V3)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG – Filtered QRS duration (fQRS) ≥ 114 ms – Duration of terminal QRS < 40 μV (low-amplitude signal duration) ≥ 38 ms – Root-mean-square voltage of terminal 40 ms ≤ 20 μV • Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V1, V2, or V3, in the absence of complete right bundle-branch block
Arrhythmias	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 h (Holter)

(continued)

Table 5.1 (continued)

Criteria categories	Major criteria	Minor criteria
Family history	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation[a] categorized as associated or probably associated with ARVC/D in the patient under evaluation	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; *RVOT* RV outflow tract, *BSA* body surface area, *PSAX* parasternal short-axis view, *aVF* augmented voltage unipolar left foot lead, *aVL* augmented voltage unipolar left arm lead, and *SAECG* signal averaged ECG
Adapted from Marcus et al. [37]

[a]A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree

plete right bundle branch block (RBBB) can be seen in ARVC but do not have adequate specificity for diagnostic purpose.

The epsilon wave is defined as reproducible, low-amplitude signals between the end of QRS complex to the onset of T wave. It represents delayed epicardial activation of the basal RV (near the tricuspid valve) and is associated with advanced conduction delay in the RV [27]. Although highly specific for ARVC, epsilon wave can be seen in cardiac sarcoidosis, acute myocardial infarction, and Brugada syndrome [25]. It is seen in approximately 5–20% of ARVC patients during their initial evaluation [19, 28, 29].

TAD of QRS complex is measured from the nadir of the S wave to the end of the QRS. Prolonged TAD (≥55 ms) in right precordial leads reflects delayed endocardial activation at RV outflow tract (RVOT) and basal RV inferior wall [27]. It is found in approximately 30–60% of ARVC patients during their initial evaluation [20, 28, 29].

Signal averaged ECG is a specialized ECG technique that generates averaged ECG signals by mathematically combining signals of 3 Simson's orthogonal bipolar leads: X, Y, and Z. This technique allows the detection of small amplitude, slowly conducting signals from pathologic myocardium ("late potentials") by analyzing filtered QRS duration (fQRSD), low amplitude signal duration below 40 μV (LAS) and root mean square voltage in last 40 ms of the QRS (RMS-40). In a study comparing signal averaged ECG in ARVC patients and healthy control, the detection of late potentials by fQRSD >114 ms, LAS > 38 ms, and RMS-40 < 20 μV was found to be high specificity for the diagnosis of ARVC [30].

The only repolarization abnormality incorporated in the revised Task Force diagnostic criteria is T-wave inversion. T-wave inversion can be seen in leads V1 and, sometimes V2, in healthy adults but rarely extends to V3 [31]. In ARVC

patients, T wave inversion in V1–V3 can be seen in approximately 30–80% patients during their initial evaluation [19, 20, 28, 29] and reflects RV dilation [14]. Other pathologic conditions that can cause T wave inversion in right precordial leads include RV cardiomyopathies from other causes, RBBB, and acute pulmonary embolism [14].

5.5.2 *Cardiac Imaging*

Echocardiography is generally the first imaging study used to evaluate suspected patients given its low cost and broad availability. Abnormal cardiac morphology and function associated with ARVC, such as RV dilation, global systolic dysfunction, and regional wall motion abnormalities can be detected by two dimensional (2D) echocardiography. The revised task force criteria rely on various degrees of these echocardiographic abnormalities to diagnose ARVC (see Table 5.1). However, evaluation of RV abnormalities by standard 2D echocardiography is limited by the retrosternal location and complex geometry of the RV as well as the RV wall motion assessment [14, 32, 33]. Three dimensional (3D) echocardiography [34] and assessment of tissue deformity by quantitative techniques, such as tissue Doppler imaging and strain imaging [35, 36] have been developed to overcome these limitations. However, whether addition of these newer techniques improve diagnostic accuracy beyond standard 2D echocardiography in ARVC patients remains to be validated.

Cardiac magnetic resonance imaging (MRI) techniques can characterize myocardial tissue composition in addition to cardiac morphology and function. However, the use of cardiac MRI to detect the fibrofatty replacement of RV myocardium (Fig. 5.4) is limited by inadequate specificity of such findings (fat infiltration of RV myocardium can be seen in healthy population) and the technical challenges of detecting fibrosis in thin RV wall by current MRI techniques [32]. Currently, the diagnosis of ARVC by cardiac MRI mainly

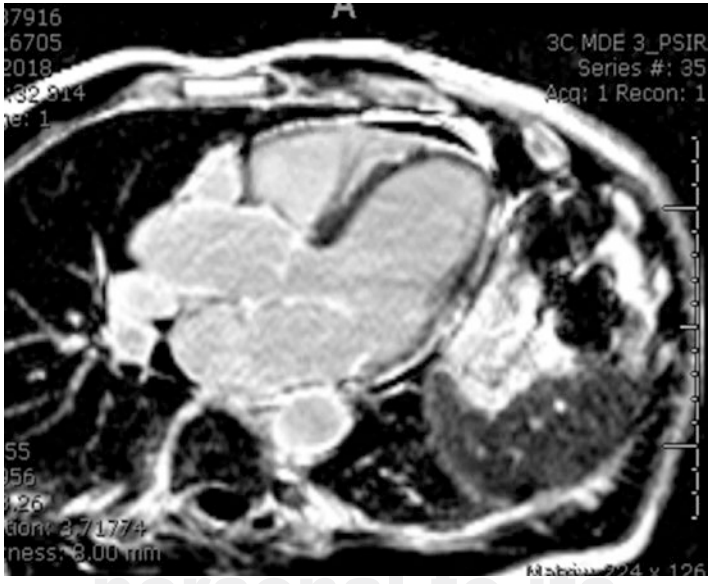

FIGURE 5.4 Subepicardial late gadolinium enhancement (LGE). Cardiac MRI from a *different* patient with ARVC demonstrates diffuse subepicardial LGE on both LV and RV. Although this finding represents myocardial fibrofatty replacement due to pathological process of ARVC in this particular patient, subepicardial LGE is not specific for ARVC and is not part of the diagnostic criteria

relies on the demonstration of regional wall motion abnormalities in association with RV dilation or global systolic dysfunction (see Table 5.1) [37]. The main advantage of cardiac MRI over echocardiogram is that the assessment of right ventricular structure and function is less limited by the retrosternal location and complex geometry of the RV. However, similar to echocardiogram, the evaluation of regional wall motion abnormalities by cardiac MRI remains challenging and is limited by subjectivity. Cardiac MRI tissue tracking technique can quantify regional ventricular function and may overcome this limitation [37].

5.5.3 *Electrophysiologic Study (EPS)*

EPS can demonstrate areas of low-voltage electrogram in the RV (reflecting RV myocardium loss) (Fig. 5.5), right ventricular VT with macroscopic re-entry mechanism, and multiple inducible right ventricular VT morphologies. These findings support the diagnosis of ARVC in suspected patients [38, 39]. In addition, the demonstration of inducible VT in ARVC patients can facilitate SCD risk stratification and guide ICD decision (see Table 5.2). EPS is generally most useful in patients with uncertain diagnosis or SCD risk despite comprehensive non-invasive testing and in patients that catheter ablation is planned.

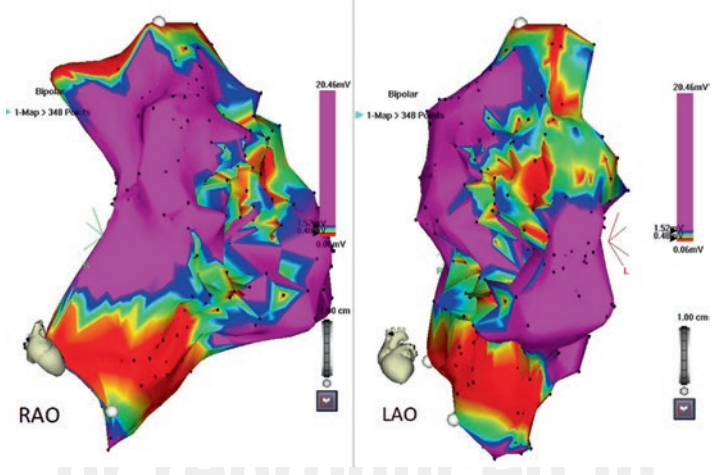

FIGURE 5.5 Low voltage areas on RV endocardial surface. Right anterior oblique (RAO) and left anterior oblique (LAO) views of endocardial RV bipolar voltage mapping from a *different* patient with ARVC demonstrates low voltage areas (<1.5 mV, represented by non-purple colors) on RV apex, inflow, and outflow tracts

Table 5.2 HRS expert consensus statement recommendations on ICD implantation in patients with ARVC

Class I	Class IIa	Class IIb
An ICD is recommended in patients with ARVC • Who have suffered a cardiac arrest with VT or VF • Who have sustained VT not hemodynamically tolerated • Or with LVEF 35% or lower and NYHA class II–III symptoms and an expected meaningful survival of greater than 1 year	An ICD is reasonable in patients with ARVC • Who have syncope suspected to be due to a ventricular arrhythmia • With hemodynamically tolerated sustained VT • With LVEF 35% or lower and NYHA class I symptoms and an expected meaningful survival of greater than 1 year • With three major, two major and two minor, or one major and 4 minor risk factors for ventricular arrhythmia[a] • With phospholamban mutation and LVEF<45% or NSVT • With Lamin A/C mutation and two or more of the following: LVEF<45%, NSVT, male sex • Or with Lamin A/C mutation and an indication for pacing	An ICD may be reasonable in patients with ARVC and two major, one major and two minor, or 4 minor risk factors for ventricular arrhythmia[a]

Adapted from Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy. Heart Rhythm. 2019. *ICD* implantable cardioverter defibrillator, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *VT* ventricular tachycardia, *VF* ventricular fibrillation, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *NSVT* non sustained ventricular tachycardia

[a]Major criteria: NSVT, inducibility to VT at EPS, LVEF ≤ 49%. Minor criteria: male sex, >1000 premature ventricular contractions (PVCs)/24 h, RV dysfunction (as per major criteria of the 2010 Task Force Criteria, see Table 5.1), proband status, 2 or more desmosomal variants. If both NSVT and PVC criteria are present, then only NSVT can be used

5.5.4 *Endomyocardial Biopsy*

Histological examination of biopsied endomyocardial tissue can demonstrate (1) the degree of myocardium loss and fibrosis, which forms the basis of diagnostic criteria for ARVC (see Table 5.1), and (2) other pathological conditions, such as myocarditis or sarcoidosis, that may mimic ARVC. Conventional RV septal biopsy has limited sensitivity to diagnose ARVC given the segmental nature of the disease and its predominant RV free wall involvement [40]. Electroanatomic mapping or cardiac imaging can be used to identify affected areas and guide the biopsy to improve diagnostic yield [40]. Endomyocardial biopsy is generally performed when the diagnosis remains uncertain despite comprehensive non-invasive testing.

5.5.5 *Genetic Testing*

The main purpose of genetic testing in ARVC patients is to support the diagnosis when a pathogenic mutation is demonstrated in suspected patients and to facilitate family member screening in ARVC patients with pathogenic mutations. Genetic testing may also be used to facilitate phenotype risk stratification in certain scenarios (see Table 5.2) [1]. To be considered pathogenic and fulfill a major diagnostic criteria, the identified mutations must be categorized as associated or probably associated with ARVC, which are defined as American College of Medical Genetics and Genomics (ACMG) class 5 (>95% likelihood of being pathogenic) or class 4 (>90% likelihood of being pathogenic) mutations, respectively [1].

Collectively, the presence of identifiable pathogenic mutations in patients with ARVC is associated with earlier onset of symptoms and VAs but not with cardiac death and transplantation rates [13]. Specific gene mutations have been observed to be associated with certain phenotypes and severities of ARVC. LV dysfunction is common in ARVC patients with LMNA, PLN (founder variants), TMEM43 (founder variants), DSP, DSG2, and DSC2 mutations but is

uncommon in PKP2 and JUP mutations [1, 14, 16]. Patients with LMNA, PLN, and DSP gene mutations seem to be at a higher risk of Vas [1, 14, 16]. In addition, those with more than one pathogenic mutation have a higher risk of developing VAs, LV dysfunction, and heart failure [1, 14, 16].

The specific intricacies and methods of genetic testing are beyond the scope of this article. In general, the genetic testing should be done by a team of providers with expertise in genetics and cardiology. The genes tested should be focused on those with sufficient evidence to be ARVC-related [1].

5.6 What Is the Diagnostic Criteria and Differential Diagnosis of ARVC?

A definitive pathological diagnosis of ARVC is based on histological demonstration of transmural fibrofatty replacement of right ventricular myocardium [41]. This method requires a sizable piece of myocardial tissue; thus, it is not clinically feasible in most patients. Given the lack of a "gold standard" clinical test, the clinical diagnosis of ARVC relies on a set of criteria. The international task force criteria were revised in 2010 to improve its sensitivity to diagnose ARVC and utilizes six categories of major and minor criteria to diagnose ARVC (see Table 5.1) [37]. The diagnosis of definite ARVC is based on fulfilling 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline ARVC: 1 major and 1 minor or 3 minor criteria from different categories; and possible ARVC: 1 major or 2 minor criteria from different categories.

ARVC should be suspected in apparently healthy patients who developed VAs, especially those originating from the RV. The diagnosis is relatively straightforward in patients with LBBB-like morphology/superior axis VAs, characteristic ECG abnormalities, and/or consistent RV abnormalities on imaging. In those with LBBB-like morphology/inferior axis VA without major ECG or echocardiographic abnormalities, the diagnosis is more challenging. The majority of these patients have idiopathic RV outflow tract (RVOT) VA and

are unlikely to benefit from more exhaustive evaluation. However, in those with family history of ARVC and/or SCD as well as those with VA features not typical for idiopathic RVOT (intrinsicoid deflection time >80 ms, QS pattern in lead V1, and/or QRS axis >90° [42]), additional evaluation with cardiac MRI, EPS, and/or endomyocardial biopsy may be pursued. In patients who undergo EPS, ARVC should also be considered when macroscopic re-entry mechanism of VT, multiple inducible VT morphologies, and low-voltage electrogram are demonstrated [38]. In rare circumstances, cardiac sarcoidosis involving the RV has been reported to mimic ARVC and idiopathic RVOT VA [43, 44]. Extracardiac manifestation and the presence of AV block can be a clue to consider cardiac sarcoidosis (Figs. 5.6 and 5.7).

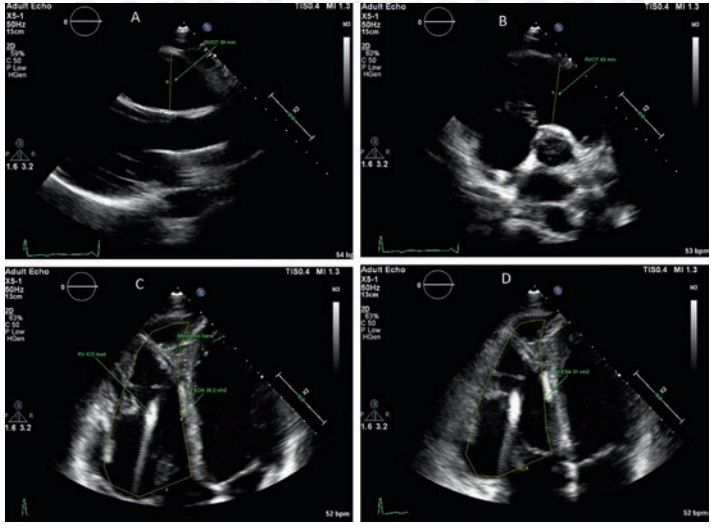

Figure 5.6 Echocardiographic criteria for ARVC. (**a**) Parasternal long-axis view demonstrates RVOT diameter of 39 mm. (**b**) Parasternal short-axis view demonstrates RVOT diameter of 43 mm. (**c**, **d**) RV focused four-chamber views demonstrates severely dilated RV with RV EDA of 36.2 cm^2 and ESA of 31 cm^2. PLAX indicates parasternal long-axis view; *PSAX* parasternal short-axis view, *RVOT* RV outflow tract, *EDA* end-diastolic area, *ESA* end-systolic area

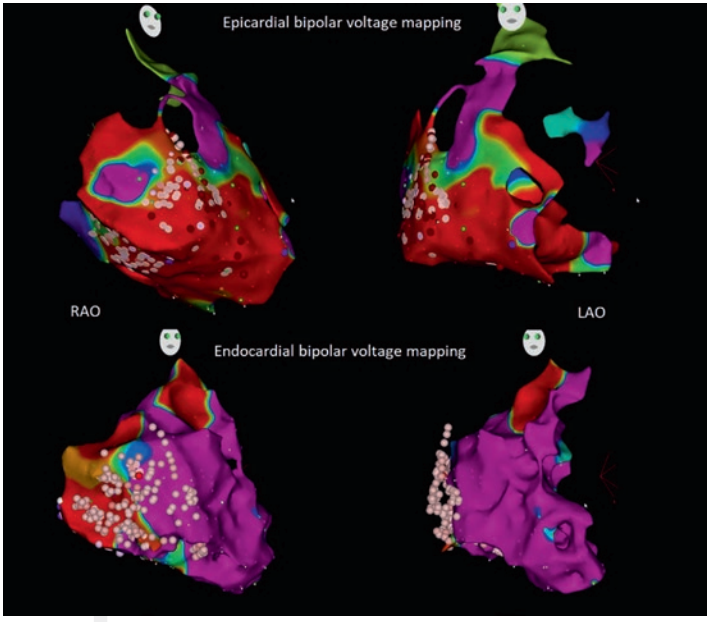

FIGURE 5.7 Low voltage areas demonstrated on both RV epicardial and endocardial surfaces. Right anterior oblique (RAO) and left anterior oblique (LAO) views of epicardial and endocardial RV bipolar voltage mapping. The low voltage areas (<1.5 mV) are represented by non-purple colors

In patients that were incidentally found to have abnormal right ventricular morphology and/or function on imaging studies, congenital heart disease with right ventricular volume and/or pressure overload, pulmonary hypertension, RV infarction, and other cardiomyopathies that may involve the RV should also be considered in addition to ARVC. If the diagnosis remains unclear after reviewing the initial imaging studies, additional imaging with different modalities and/or cardiac catheterization can be helpful. Lastly, patients with advanced stage ARVC can have significant LV involvement and may present with heart failure symptoms. The differential in this scenario is broad, and other causes of left ventricular cardiomyopathy need to be considered.

5.7 How Are Patients Selected for ICD Implantation?

The use of an ICD is associated with significant reductions in SCD in a large cohort study of patients with ARVC [13]. Although data from randomized controlled studies are lacking, an ICD is likely valid given that the patients who were selected to receive an ICD are generally perceived to be at higher risk; thus, biasing against the effectiveness of ICD. As ICD only benefits patients who will develop SCD and is associated with significant cost and complications, SCD risk stratification is necessary. A previous history of sustained VA, especially those associated with hemodynamic instability, is the most important risk factor [45]. Other risk factors include significant RV and LV dysfunction, history of cardiac syncope, non-sustained VT, frequent PVCs on 24-h Holter, male sex, and certain high-risk genetic mutations [45]. The HRS Expert Consensus Statement recommended ICD implantation in ARVC patients who have suffered a VT/VF cardiac arrest, have sustained VT (not hemodynamically tolerated), with LVEF 35% or lower, NYHA class II–III symptoms, and an expected meaningful survival of greater than 1 year [1]. Table 5.2 lists other recommendations regarding ICD implantation in ARVC patients.

5.8 What Is the Management of ARVC?

Competitive sport and high intensity endurance exercises are associated with increased risk of VA, SCD, and progression of structural changes in ARVC patients [18, 46]; Thus, participation in such activities should be avoided by the patients [1, 47]. Participation in recreational sport with a limited exertional component likely does not increase these risks [46].

Antiarrhythmic drugs have been used to decrease VA in ARVC patients based on the results of non-randomized studies and anecdotal experiences given the lack of data from randomized controlled studies. Amiodarone and sotalol have

been inconsistently associated with VA suppression (approximately 70–80%) in ARVC patients [29, 48, 49] and have been suggested by the HRS expert consensus to be used to control arrhythmic symptoms or reduce ICD shocks (class IIb) [1]. As VA and SCD in ARVC frequently occur with adrenergic stimulation, such as during exercise, the use of beta blocker has been recommended by some experts [47]. However, the benefit of beta blocker in reducing life-threatening arrhythmic event has not been demonstrated [29].

There is also a paucity of data demonstrating the efficacy of medications in improving the RV function or slowing the progression of right ventricular failure in ARVC patients. An animal model demonstrated that preload-reduction using a combination of diuretics and isosorbide dinitrate prevented the development of ARVC induced by endurance exercise training [50]; thus, HRS expert consensus suggests that the use of isosorbide dinitrate to reduce preload may be considered in symptomatic ARVC patients with RV dysfunction [1]. Medical treatment to optimize volume status and slow/improve LV dysfunction in ARVC patients is similar to that of heart failure due to other conditions. However, there are some that advocate beta-blockers for all patients with ARVC, regardless of LVEF, to both reduce arrhythmias and prevent RV and LV dysfunction. In addition, and somewhat unique to ARVC is the exercise restriction. It is reasonably well established that more than moderate intensity exercises increases the risk of the development of heart failure.

5.9 What Is the Role of Catheter Ablation?

Catheter ablation aims to eliminate scar-related reentry circuit of VT. It is generally recommended in patients who have failed or unable to tolerate to antiarrhythmic drugs. However, if antiarrhythmic drugs are not desired, it can be used as a first line treatment [51]. In ARVC patients with VT, VT-free survival after at least one catheter ablation was reported to be 83% and 56% after 1 and 3 years, respectively [52, 53]. As

subepicardial scar is usually more prominent in ARVC, combined epicardial and endocardial ablation has been shown to be superior to endocardial only ablation (approximately 40% reduction in VT recurrence [54]) but is associated with higher risk of acute procedural complications [54]. Combined epicardial and endocardial ablation has been recommended as the initial ablation strategy by some experts [47].

5.10 What Are the Recommendations for Screening of Family Members?

As ARVC is mostly transmitted in an autosomal dominant pattern, HRS expert consensus statement recommends that first-degree relatives of ARVC patients (proband) undergo clinical evaluation every 1–3 years starting at 10–12 years of age. The evaluation should include 12-lead ECG, ambulatory ECG, and cardiac imaging. If the ARVC patient (proband) has identifiable pathogenic mutations (ACMG class 4 or 5 mutations), genetic testing can be used to facilitate family member screening. In this case, it may be reasonable for asymptomatic members of a family who do not have the familial variant and have a normal cardiovascular evaluation to be released from regular screening and educated to return if disease symptoms occur [1].

5.10.1 Case Conclusion

After initial evaluation, the patient met 1 major (T wave inversion in V1–V3) and 1 minor diagnostic criteria (non-sustained VT with LBBB-like morphology/inferior axis) for ARVC. At this point, cardiac imaging was needed to evaluate for structural abnormalities that would support our suspicion for ARVC or suggest an alternative diagnosis. TTE was obtained and demonstrated (1) severely dilated RV with RVOT diameter of 39 and 43 mm in parasternal long and short axis views, respectively (Fig. 5.4), (2) severe RV systolic

dysfunction with fractional area change of 14% (Fig. 5.4). (3) Akinetic RV apical and inferior walls (other RV walls are severely hypokinetic). Of note, LV size and systolic function were normal. As TTE findings fulfilled additional major diagnostic criteria, the diagnosis of definite ARVC was made. In fact, this patient subsequently fulfilled 3 major criteria as the genetic screening test also showed heterozygous PKP2 disease causing mutation (c.2146-1 G>C). Neither cardiac MRI nor endomyocardial biopsy was obtained as the diagnosis of ARVC was quite certain and the patient already had an ICD (he is unquestionably high risk for SCD).

This patient had recurrent VT causing multiple ICD shocks despite taking amiodarone. We initially increased his amiodarone for acute VT control. However, neither increasing amiodarone dose nor switching to sotalol would be an optimal long-term strategy given side effects of amiodarone and questionable incremental efficacy of sotalol. Thus, we decided to perform combined epicardial and endocardial EPS with plan for an ablation. Bipolar voltage mapping during EPS showed areas of low voltage electrograms (<1.5 mV) along the free wall, apex, and inferior wall on RV epicardium as well as inferior wall of RV endocardium (Fig. 5.5). Several different VTs were induced and mapped to multiple epicardial RV locations. Overall result of EPS was consistent with ARVC. Extensive ablation was performed on these areas. After the ablation, amiodarone was gradually reduced to 100 mg/day over the following 6 months. The patient had no recurrent VT after 12 months of follow up. He walks in a park for exercise but avoids higher intensity endurance exercise.

Clinical Pearls

- ARVC is a genetic cardiomyopathy caused by pathogenic mutations in genes encoding components of intercalated discs, such as desmosomes.
- ARVC most commonly presents with symptoms of ventricular arrhythmias, such as palpitations, presyncope, syncope, and SCD.

- Heart failure symptoms, especially right-sided, may develop later in the course of ARVC.
- ARVC is diagnosed by a set of criteria incorporating ECG, cardiac imaging, and genetic findings.
- ICD implantation and avoiding high intensity endurance exercise play a central role in reducing sudden cardiac death risk.

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