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Arrhythmogenic right ventricular cardiomyopathy

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Abstract

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive cardiomyopathy characterized by fibrofatty infiltration of the myocardium, ventricular arrhythmias, sudden death, and heart failure. ARVC may be an important cause of syncope, sudden death, ventricular arrhythmias, and/or wall motion abnormalities, especially in the young. As the first symptom is sudden death or cardiac arrest in many cases, an early diagnosis and risk stratification are important. Recent advances in diagnostic modalities will be helpful in the early diagnosis and proper management of patients at risk. Restriction of strenuous exercise and implantation of implantable cardioverter-defibrillators are important in addition to medical treatment and catheter ablation of ventricular tachycardia. Recently introduced genetic screening may help to identify asymptomatic carriers with a risk of a disease progression and sudden death.

KEYWORDS
arrhythmia, arrhythmogenic right ventricular cardiomyopathy, cardiomyopathy

1 | INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a kind of cardiomyopathy characterized by progressive, fibrofatty replacement of the right ventricle (RV), and life-threatening ventricular arrhythmias with left bundle branch block (LBBB) morphology.[1-4]

With the wider application of diagnostic modalities such as 2D echocardiography, cardiac magnetic resonance (MR), and genetic testing to patients with ventricular arrhythmias, more patients with ventricular arrhythmias are diagnosed as ARVC. The managements of such patients, especially asymptomatic, are complex with risk stratification, lifestyle modification, and family screening. As most clinicians have very limited experience in management of patients with ARVC, decision making may perplexing.

Arrhythmogenic right ventricular cardiomyopathy is a familial disease in approximately 50% of cases and is typically transmitted as an autosomal-dominant trait with variable penetrance. ARVC has an estimated prevalence of 1 in 5000 in the general population and much higher in some areas such as Padua, Italy.[3,5,6] However, the age-dependent penetrance and variable expression make the true prevalence difficult to estimate. The different prevalence of the disease observed in different parts of the world could be due either to clustering of the disease in some geographic areas or underdiagnoses.

2 | PATHOGENESIS

2.1 | Genetic background

Arrhythmogenic right ventricular cardiomyopathy is considered as a disease of the desmosome. Desmosomes are abundant in the skin and myocardium and contribute mechanical attachment between cells and are also important mediators of the intracellular and intercellular signal transduction. Desmosomes are composed of plakoglobin, plakophilins, desmoplakin, desmogleins, and desmocollins (Figure 1).[3] In most cases, ARVC is caused by mutations in genes encoding for desmosomal proteins: plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP2), desmoglein-2 (DSG2), and desmocollin-2 (DSC2).[7,8] A minority of cases is caused by mutations in nondesmosomal genes.

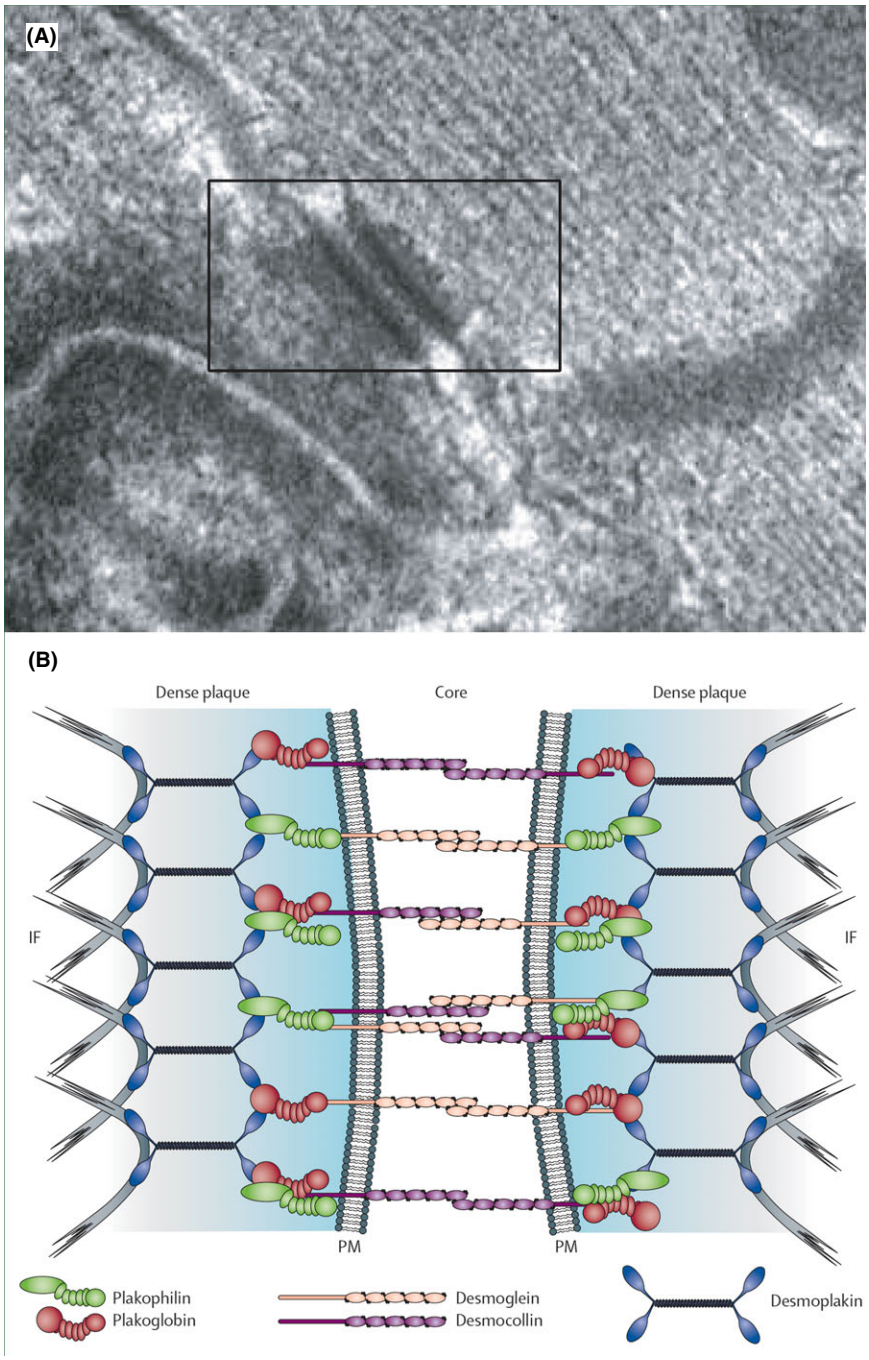

FIGURE 1 Intercellular mechanical junction (desmosome) of the cardiomyocyte (A) Transmission electron microscopy of cardiomyocyte desmosome (boxed area, ×80 000). B, Schematic representation of desmosome components. Core region mediates cell-cell adhesion, and dense plaque provides attachment to the intermediate filaments. There are 3 major groups of desmosomal proteins: transmembrane proteins (desmosomal cadherins) including desmocollins and desmogleins; desmoplakin, a plakin family protein that binds directly to intermediate filaments (desmin in the heart); and linker proteins (armadillo family proteins) including plakoglobin and plakophilins, which mediate interactions between the desmosomal cadherin tails and desmoplakin. IF, intermediate filaments; PM, plasma membrane. Reproduced with permission from Basso et al[3]

Intercellular junction is disrupted due to abnormal desmosomes, especially under increased mechanical stress. The canonical Wnt-β-catenin signaling pathway is also involved in the pathogenesis of ARVC. β-catenin interacts with members of the TCF-LET (T-cell factor–lymphocyte-enhancing factor) family of transcriptional factors and suppresses the differentiation of mesodermal precursors into adipocytes and fibrocytes by suppressing the expression of adipogenic and fibrogenic genes.[9] With abnormal desmosomal assembly, plakoglobin is translocated from the sarcolemma to the nucleus and antagonize the effects of β-catenin. Then, plakoglobin suppresses Wnt-β-catenin signaling and increases the expression of adipogenic and fibrogenic genes. Finally, typical fibrofatty changes develop.[10]

Arrhythmogenic right ventricular cardiomyopathy is mostly transmitted as an autosomal-dominant trait. Autosomal-recessive forms are rare, mostly in the cardiocutaneous syndromes such as Carvajal syndrome and Naxos disease.[8] Many studies showed that compound and digenic heterozygosity were common and these multiple mutations were associated with earlier manifestation and more malignant phenotype, suggesting "digenic heterozygosity".[11-13] Recently published animal study demonstrated that loss of PKP2 only in adult myocyte was sufficient for the development of an arrhythmia without overt structural disease, that later gives way to an ARVC and finally, a biventricular dilated cardiomyopathy (DCM).[14]

2.2 | Pathology

Progressive myocardial cell death and subsequent fibrofatty infiltration are the primary findings in ARVC. Fibrofatty infiltration starts from the epicardium, then extends to the endocardium and leads to wall thinning and aneurysmal changes especially in the RV inlet, RV outlet, and apex; the so-called triad.[1,2,15] This concept now changed with the demonstration of a high prevalence of left ventricular (LV) involvement.[13,15-19] The fibrofatty infiltration also slows down electrical conduction, and ventricular tachyarrhythmias may develop. Recent study showed that fibrosis occurs after mechanical dysfunction is detected, suggesting that the fibrosis may reparative.[14]

Arrhythmogenic right ventricular cardiomyopathy was initially considered as a developmental defect of the RV myocardium, that is, dysplasia.[1] However, ARVC is now considered as a genetically determined cardiomyopathy.[15] In some patients, inflammatory infiltrations are associated with fibrofatty infiltrations.[6,15,20,21]

The onset of the disease from the teenage years onward might be related to the completion of intercalated disk maturation, or the need for exposure to a certain amount of exercise before ARVC becomes manifest.[4] Some stages have been suggested in the natural history of ARVC. In the early "concealed phase," a structural change is absent or minor, but patients may be at risk of SCD caused by sustained VT or ventricular fibrillation (VF) similar to ion channel disease.[3,14,22,23] The study of Cerrone et al[24] suggested that fibrofatty changes may be preceded by gap-junction remodeling, which is associated with a reduction in the amplitude of the sodium current, slowed conduction, and an increased propensity for ventricular arrhythmias and these could occur in the absence of detectable structural disease, similar to the concealed phase of ARVC. PKP2 mutation-associated impaired sodium current could yield a Brugada syndrome phenotype.[22] Most SCDs occur during ordinary daily activities.[16,20]

In the overt "electric phase," patients show ventricular arrhythmias with manifested structural abnormalities of the ventricles. Patients may suffer from a VT, but with a lower risk of SCD than patients with the early concealed phase. In a large transatlantic study, the median age of patients with monomorphic VT was 36 years, 13 years more than those with SCD.[25]

In the later phase, patients suffer from heart failure, ventricular arrhythmias, and thromboembolisms. Recent study showed that about one-fifth of their patients presented after 50 years old and presented predominantly with sustained VT and were less likely to have prior syncope, ECG changes, ventricular ectopy, or identifiable pathogenic mutations, and more atrial arrhythmias than patients with early presentation.[26]

3 | CLINICAL PRESENTATION

The clinical presentation is diverse, from exercise-related SCD as the first symptom in the young, to biventricular heart failure in the elderly. Most patients with ARVC come to medical attention because of ventricular arrhythmias and/or ECG abnormalities. The disease expression is highly variable, even among subjects from the same family or those carrying the same mutation. Half of ARVC cases are considered as familial with an autosomal-dominant inheritance with incomplete penetrance and variable expressivity. That suggests the influence of environmental factors and other genetic modifiers in the manifestation of ARVC such as age-related progression, sex-hormone differences, differences in the amount and intensity of strenuous exercise, and the presence of other modifier genes.

Arrhythmogenic right ventricular cardiomyopathy is an important cause of SCD, especially in young adults.[16,20] Clinical manifestations, including palpitation, syncope, VT, and SCD, usually develop between the second and fourth decades of life.[4,17,25] The risk of life-threatening arrhythmias reaches its peak between ages 21 to 40 years as 4.0 per 100 person-years.[23] The patients with a pediatric onset were typically male mutation carriers and were more likely to present with SCD or an aborted cardiac arrest, whereas adults more often presented with sustained VT.[27] Recent Japanese study showed that radical mutation carriers exhibited earlier onset of lethal ventricular arrhythmias than missense mutation carriers or mutation-negative patients.[28]

The disease is more prevalent, earlier onset and is more malignant in its arrhythmic expression in men than in women, which can be explained by the influence of sex hormones and the differences in the amount and intensity of exercise.[6,25,29,30] Previous study suggested no significant gender difference in the occurrence of heart failure and LV dysfunction.[25] However, a recent Japanese study showed significantly higher risk of heart failure death or heart transplantation in female.[29] These discrepancies were explained by no inclusion of family members, longer follow-up, and smaller body surface area of patients in Japanese study.[29]

At least half of patients have normal findings on physical examination.[1] With progressive RV dilation, a tricuspid regurgitation murmur and giant a wave may be observed. About one-third to half of patients with ARVC have a normal ECG. More than half of patients have ventricular arrhythmias of an RV origin and these ventricular arrhythmias show multiple QRS morphologies in many cases.[7] The most common repolarization abnormality is T-wave inversion in V_1 to V_3. Sometimes, epsilon wave is seen in the right precordial leads. A minority of patients exhibit ECG and clinical features of Brugada syndrome.[31]

Arrhythmogenic right ventricular cardiomyopathy seems to be responsible for some unexpected perioperative deaths.[20] Most pregnancies were tolerated well.[32] One autopsy study showed that 2 of 200 cases of SCD associated with ARVC occurred after childbirth.[20]

Atrial arrhythmias are common in patients with ARVC and present at a younger age than in the general population.[23,33] Atrial arrhythmias are clinically important as they are associated with inappropriate ICD shocks and an increased risk of both SCDs and heart failure.

A previous study showed that LV involvement was age dependent and usually seen in patients with a late stage.[2] However, biventricular or left dominant forms can be observed in any stage of the

disease with the aid of cardiac MR nowadays.[18,19,34] Some think that it may be more appropriate to use the broader term "arrhythmogenic cardiomyopathy" instead of ARVC.[34] A left dominant form of ARVC is observed in a minority of cases. The left dominant form is characterized by right bundle branch block (RBBB)-type ventricular arrhythmias, T-wave inversion in the inferior or lateral leads, and LV dysfunction.[34] A left dominant form is more commonly seen in patients with DSP and DSG2 mutations than in patients with PKP2 mutation.[12,13,19,25] One Chinese study showed that LV involvement could be a sign of a nonsense desmosomal gene mutation.[17]

4 | DIAGNOSIS

Arrhythmogenic right ventricular cardiomyopathy should be suspected in all young patients with syncope, VT, or cardiac arrest. The International Task Force Criteria based on structural, histologic, ECG, arrhythmic, and familial features were introduced in 1994.[35] Unfortunately, this criteria lacked sensitivity for early and familial disease.[35] In 2010, the diagnostic criteria were revised to improve the diagnostic sensitivity, while maintaining the specificity (Table 1).[36] The modified criteria included qualitative in addition to quantitative data and new diagnostic modalities such as cardiac MR and genetic test. However, even with new criteria, the diagnosis remains problematic.[37] Unfortunately, the modified criteria are not touching a left dominant form and cannot differentiate sarcoidosis from ARVC.[34,38,39] Diagnosis was considered definite when 2 major, or 1 major and 2 minor criteria, or 4 minor criteria from different categories, were fulfilled. Diagnosis was considered borderline when 1 major and 1 minor or 3 minor criteria from different categories were fulfilled. Diagnosis was considered possible when 1 major or 2 minor criteria from different categories were fulfilled.

Epsilon waves, T-wave inversion in V_1-V_3, a QRS duration ≥110 ms in V_1-V_3, and a prolonged S-wave upstroke in V_1-V_3 ≥55 ms were common ECG findings among patients with ARVC (Figure 2), and a prolonged S-wave upstroke in V_1-V_3 ≥55 ms was the most frequent ECG finding and may be considered as a sensitive and specific marker for the diagnosis of ARVC.[40] ECG abnormalities such as epsilon wave, T-wave inversion, and late potential are more frequently observed in patients' multiple desmosomal gene mutations.[13] As the interobserver variability in the assessment of the epsilon waves is high, caution is needed.

The RV size and function are usually evaluated using a variety of imaging modalities, including 2D echocardiography and cardiac MR. RV angiography and computed tomography are rarely used nowadays. Two-dimensional echocardiography and cardiac MR are the most commonly used imaging modality as they are noninvasive, widely available, radiation free (Figures 3 and 4), and Revised Task Force Criteria contain mostly 2D echocardiography and cardiac MR criteria.[18,36,41] Typical morphological features are regional RV akinesia, dyskinesia, aneurysm, or dyssynchronous contraction. A quantitative assessment of the RV function is challenging due to complex anatomy and load dependency of the RV and requires high expertise.

Multiple VTs induced during electrophysiologic study suggest underlying ARVC. One Chinese study showed that subjects with mutations not only had a higher proportion of VT history, but also a higher ratio of fast VT (≥200 bpm) induced during electrophysiologic test.[42] The isoproterenol infusion test is highly sensitive for the diagnosis of ARVC, particularly in its early stages.[43]

Histologic confirmation of pathology is essential in suspected cases of ARVC when all noninvasive evaluations are ambiguous (Figure 5). The sensitivity of endomyocardial biopsy (EMB) in a simulated study using explanted heart varied from 60%-95% according to the RV sampling sites,[44] which was higher than 51% of the in vivo human study.[45] The results of simulation study showed no diagnostic value of either septal or LV biopsy, so negative septal biopsy does not exclude ARVC. However, RV septal biopsy may identify other conditions such as myocarditis or sarcoidosis.[39,46] Three-D electroanatomic voltage mapping may enhance the accuracy of the EMB by demonstrating low-voltage areas.[47] Multiple RV site biopsies including free wall are more sensitive than septal biopsy but with the risks of pericardial effusion and cardiac tamponade as 3.7% and 0.6%, respectively.[45]

About half of left dominant arrhythmogenic cardiomyopathy was misdiagnosed as viral myocarditis, DCM, hypertrophic cardiomyopathy, or idiopathic VT.[34] Due to the age-related penetrance and progressive nature of ARVC, lifelong clinical assessment at every 2-3 years from around age 11 and 12 years is warranted in healthy gene carriers and family members with a negative phenotype.[6,23]

4.1 | Genetic test

Identification of a putative gene mutation in patients with suspected ARVC is a major diagnostic criterion. Gene mutations are identified in up to 60% of patients.[4,13,17,25,28,42,48] So, the lack of an identifiable mutation does not exclude the diagnosis of ARVC. The most commonly affected gene is PKP2, followed by DSP, DSG2, JUP, and DSC2 and screening of nondesmosomal genes marginally affects the detection rate for mutations.[4,12,17,37,42,49] PKP2 mutation is the most common desmosomal gene mutation in Caucasian and Chinese studies.[4,12,17,42] However, a recent Japanese study showed that DSG2 mutation is the most common, suggested some racial difference even among Asian.[28]

In another 16%, the analysis yields variants of uncertain significance.[8,49] The signal-to-noise ratio is about 4:1, much lower than that of long QT syndrome (19:1) or catecholaminergic polymorphic VT (20:1).[8] Radical mutations have a high probability of ARVC-associated mutations, whereas rare missense mutations should be interpreted with great caution as the frequency of missense mutations was similar between probands and controls.[49] Missense mutations in Caucasian patients, within the DSP and DSG2 "hot spot," and a conserved PKP2 and DSG2 residue are more likely pathogenic.[49] Recent Japanese study showed that DSG2 mutations were almost missense, whereas over 90% of PKP2 mutations were radical.[28] Some mutations of "genetic variants of unknown significance" may act as a

TABLE 1 2010 Revised Task Force Criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy[36]

	Major	Minor
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%
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 (V_1, V_2, and V_3) or beyond in individuals >14 y of age (in the absence of complete RBBB QRS ≥120 ms)	• Inverted T-waves in leads V_1 and V_2 in individuals >14 y of age (in the absence of complete RBBB) or in V_4, V_5, or V_6 • Inverted T-waves in leads V_1, V_2, V_3, and V_4 in individuals >14 y of age in the presence of complete RBBB
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 (V_1 to V_3)	• 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 V_1, V_2, or V_3, in the absence of complete RBBB
Arrhythmias	• Nonsustained or sustained ventricular tachycardia of LBBB 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, LBBB 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)

(Continues)

TABLE 1 (Continued)

	Major	Minor
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 y 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, 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; RBBB, right bundle branch block; LBBB, left bundle branch block; ARVC, arrhythmogenic right ventricular cardiomyopathy.

Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

[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 a demonstrated linkage to the disease phenotype in a conclusive pedigree.

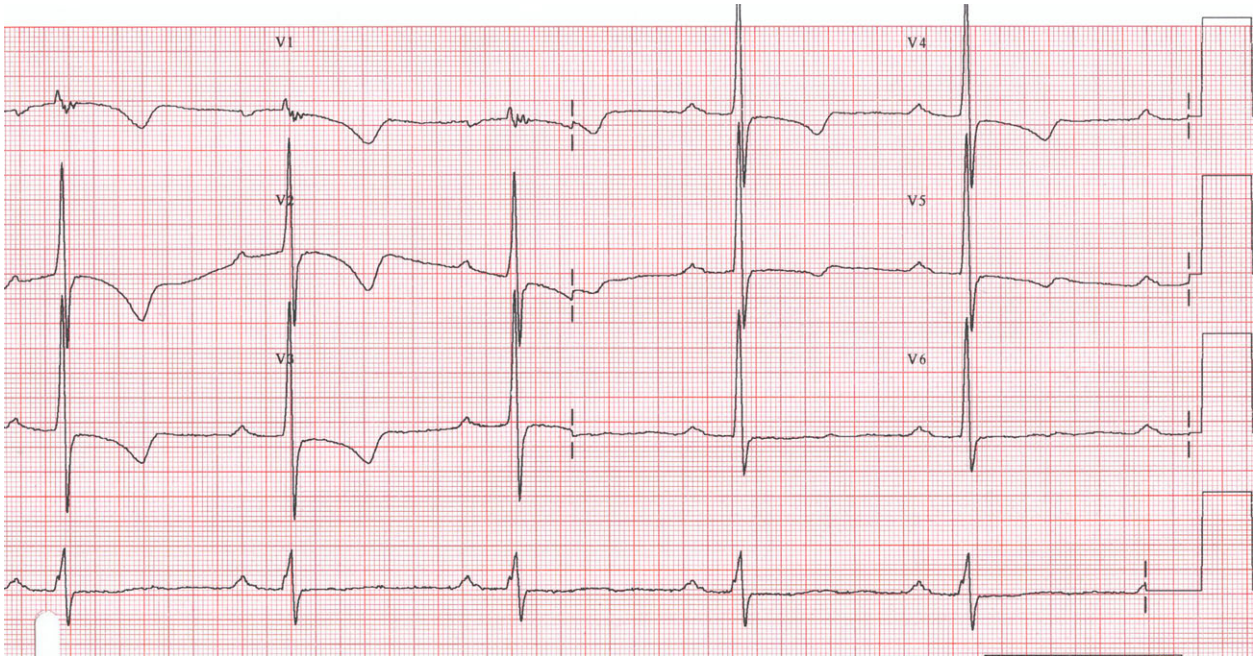

FIGURE 2 Routine ECG of a patient with arrhythmogenic right ventricular cardiomyopathy exhibiting a diffuse T-wave inversion in the precordial leads and an epsilon wave in lead V_1. 50 mm/s and 20 mm/mV

modifier. A large database of mutations has become accessible (http://www.arvcdatabase.info/), which may be of help when interpreting genetic findings.

Extreme caution is necessary regarding both obtaining a genetic test and interpreting its significance. Some experts recommend referring a patient with a questionable diagnosis of ARVC to a specialty center rather than ordering the genetic test.[8] The presence of a genetic mutation alone cannot override the clinical judgment regarding the diagnosis of ARVC, nor should the absence of a mutation in the setting of compelling clinical evidence call the diagnosis into question.[49]

4.2 | Cardiac MR

Major cardiac MR criteria are the presence of regional RV akinesia or dyskinesia or dyssynchronous RV contraction combined with 1 of the following; ratio of RV end-diastolic volume to body surface area ≥110 mL/m^2 in male (≥100 mL/m^2 in female) or RV ejection fraction ≤40%. Minor cardiac MR criteria are the presence of regional RV akinesia or dyskinesia or dyssynchronous RV contraction combined with 1 of the following; ratio of RV end-diastolic volume to body surface area ≥100 to <110 mL/m^2 in male (≥90 to <100 mL/m^2 in female) or RV ejection fraction >40% to ≤45%.[36]

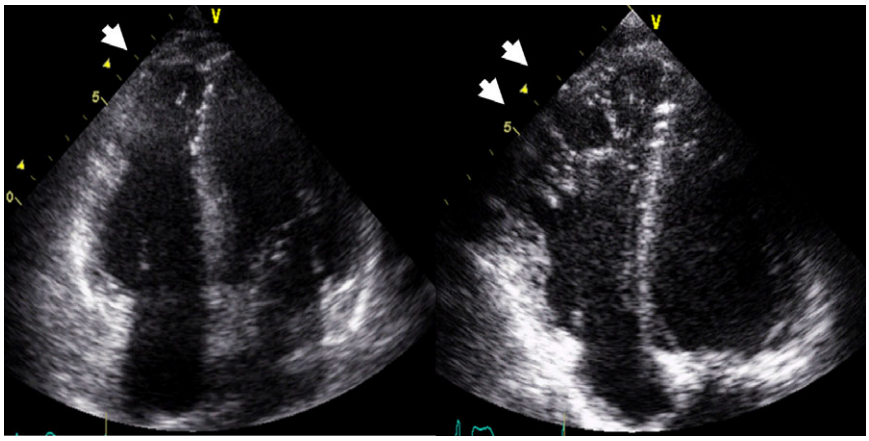

FIGURE 3 Two-dimensional echocardiography showing a localized right ventricular apical aneurysm (left) and diffuse aneurysmal changes with prominent trabeculations (right) of the right ventricle in patients with arrhythmogenic right ventricular cardiomyopathy

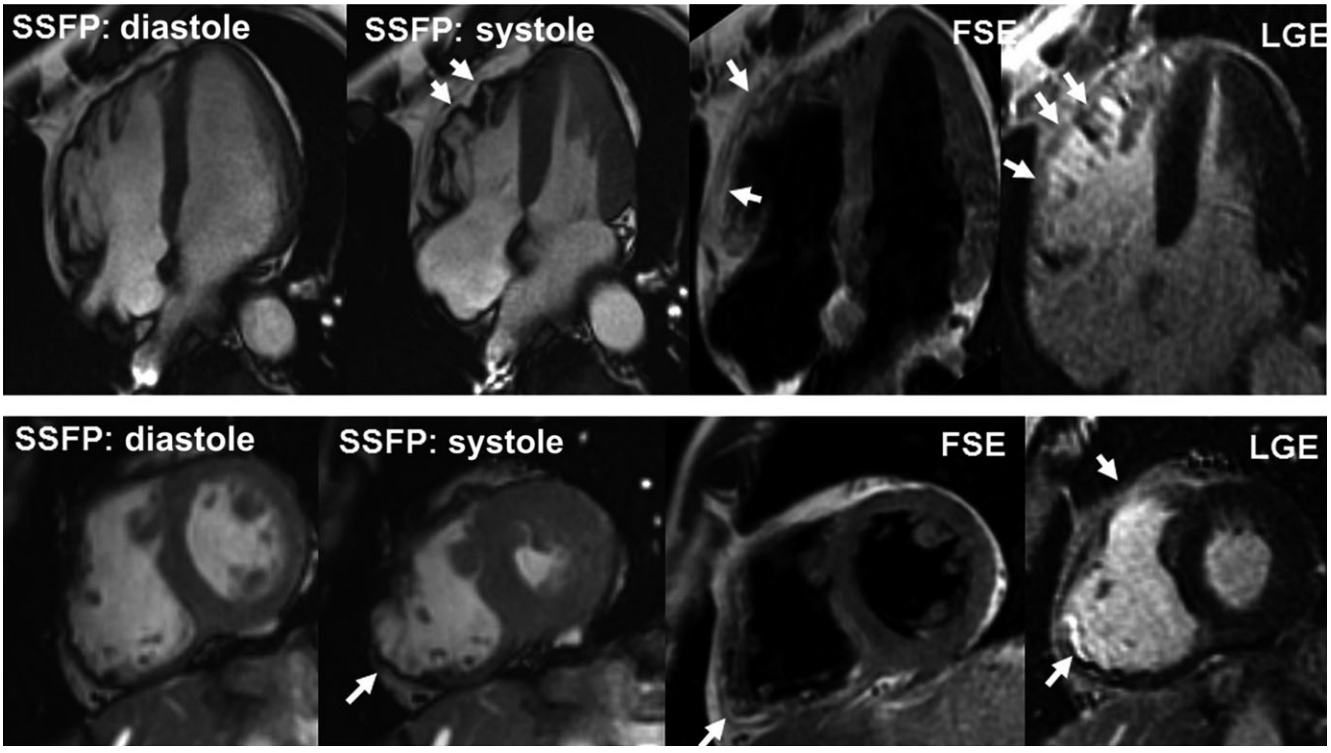

FIGURE 4 Cardiac magnetic resonance images of patient with arrhythmogenic right ventricular cardiomyopathy (ARVC). In fast imaging employing steady-state acquisition (SSFP) images, multiple dyskinetic areas of right ventricle are shown (arrows). Signs of fat infiltration in fast spin echo (FSE, arrows) and fibrosis in late gadolinium enhancement (LGE) images (arrows in LGE images) are evident. In this case, a minor Task Force Criteria was satisfied. Reproduced with permission from Aquaro et al[18]

Cardiac MR has become the preferred imaging technique because it enables visualizing both structural and functional ventricular abnormalities with the use of late gadolinium enhancement even before the development of wall thinning or motion abnormalities.[18,37,50] Unfortunately, late gadolinium enhancement is not included in the modified criteria. Recent study from Swiss showed that the modified criteria of cardiac MR showed an optimal (100%) specificity, but a poor (53%) sensitivity and the high diagnostic accuracy was achieved by the combined evaluation of wall motion abnormality with signal abnormality including fat infiltration and late gadolinium enhancement.[18] Electrical abnormalities on the ECG and Holter monitoring are known to precede detectable structural abnormalities in ARVC mutation carriers.[51] Thus, cardiac MR is probably not necessary in the absence of these electrical abnormalities.

Unfortunately, cardiac MR cannot be used in patients with claustrophobia, unstable arrhythmias, and some implanted cardiac devices. The differential diagnosis of ARVC from cardiac sarcoidosis and myocarditis by cardiac MR is challenging. Some experts think that the routine use of cardiac MR should be limited to centers with experienced specialists.

4.3 | Differential diagnosis

The differential diagnosis from other diseases may challenging in substantial cases (Table 2). The differential diagnosis of early-phase

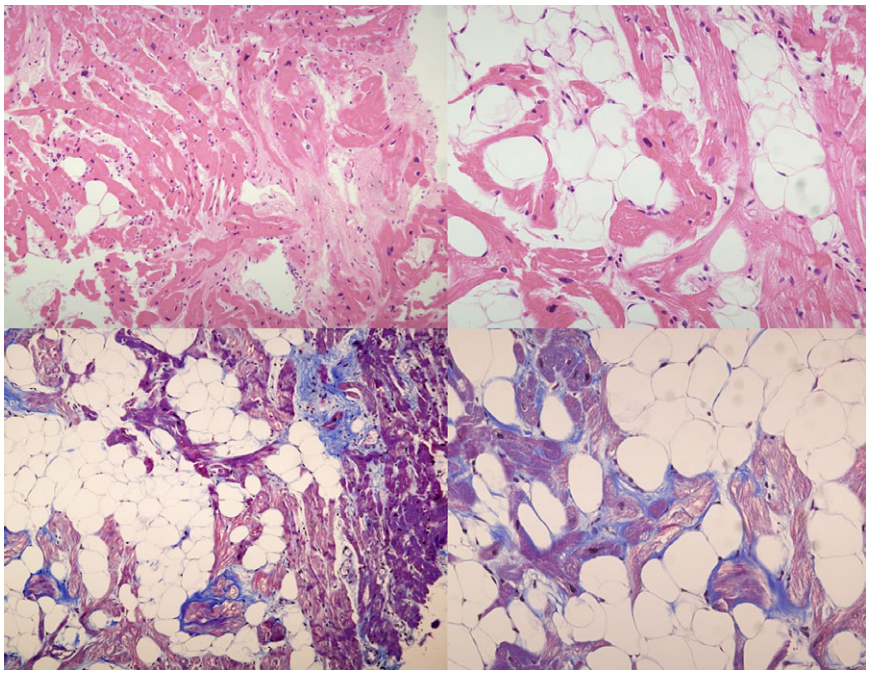

FIGURE 5 Endomyocardial biopsy findings of a patient with arrhythmogenic right ventricular cardiomyopathy (ARVC). Typical fibrofatty infiltrations are seen. Upper: Hematoxylin and eosin staining, Lower: modified Masson's trichrome staining

TABLE 2 Differential diagnosis of arrhythmogenic right ventricular cardiomyopathy

Idiopathic right ventricular outflow tract tachycardia
Sarcoidosis
Myocarditis
Dilated cardiomyopathy
Brugada syndrome
Pulmonary hypertension
Right ventricular infarction
Left to right shunts
Athlete heart
Uhl's anomaly

ARVC from RV outflow tract (RVOT) tachycardia or ectopy is confusing.[52,53] Usually, patients with idiopathic RVOT tachycardia have only one morphology, LBBB with inferior axis. However, patients with ARVC may have multiple VT morphologies, most specifically LBBB and a superior axis. Early-phase ARVC patients had a slightly lower RV function, more pronounced RV mechanical dispersion, and larger RV diameter compared with the RVOT tachycardia patients.[53] One study showed that ECG findings such as RVOT tachycardia or ectopy with a QRS duration in lead I of ≥120 ms, the earliest onset QRS in lead V_1, QRS notching, and a transition of V_5 or later predicted the presence of ARVC.[54] Another recent study showed that RVOT ectopy with an intrinsicoid deflection time >80 ms, a QS pattern in lead V_1, and QRS axis >90° suggested ectopy associated with early ARVC.[52] Some patients may have typical features of Brugada syndrome.[31] Other differential diagnoses are sarcoidosis, myocarditis, congenital abnormalities, pulmonary hypertension, RV infarct, and DCM. Sarcoidosis should be suspected in the case of an elderly onset, nonfamilial pattern, high-grade atrioventricular block, and mediastinal lymphadenopathy.[39] The clinical distinction between DCM and advanced ARVC with biventricular involvement may difficult. Myocarditis and inflammatory cardiomyopathy may be differentiated by an electroanatomic voltage mapping-guided EMB.[46,47]

5 | PROGNOSIS

As ARVC is a progressive disease, risk factors may change during the follow-up requiring a periodic revaluation of the risks. Heart failure and SCD represent the main components of the overall mortality in such patients.[29,55,56] A large (n = 1001) transatlantic study showed that during a median follow-up of 7 years, 72% of index-patients presenting alive experienced sustained ventricular arrhythmias.[4] SCD during the follow-up occurred more frequently among index-patients without an ICD, and progression of ARVC resulting in symptomatic heart failure was observed in 13% of the index-patients. Overall, cardiac mortality and the need for cardiac transplantations were low at 6% and 4%, respectively. Overall, 89% of the index-patients were alive at the last follow-up. So, the long-term outcome was favorable if timely diagnosed and appropriately treated. ICD implantations significantly reduced the SCD incidence during the follow-up and improved the long-term outcome. Index-patients with and without identified mutations had a similar disease course and outcome although the disease onset was earlier in the index-patients with mutations. The long-term outcome in the family members was negatively influenced by the symptoms at first evaluation and the presence of mutations. Recent Japanese study suggested that family members rarely developed ARVC-related symptoms,[28] and another Japanese study showed that most (84%) of deaths were due to heart failure.[56] The high prevalence of death due to heart failure may be due to aggressive therapeutic management including ICD implantation.

The annual mortality rate reported in different studies varies considerably. The adverse prognosis of ARVC patients has been overestimated by reports from tertiary referral centers with high-risk patients, and studies from community-based patient cohorts and screening of familial ARVC reported a much better prognosis.

Previously mentioned large transatlantic study showed that most (82%) of the family members were asymptomatic and had a better event-free survival than the index-patients.[4] The long-term outcome in family members was negatively influenced by symptoms at first evaluation and the presence of mutations, family members with mutations had worse clinical outcomes.[4]

6 | RISK STRATIFICATION

The prognosis of patients with ARVC largely depends on the electrical stability and ventricular function. Understanding the role of both the genetic background and environmental modifier are needed to fully understand the phenotype of patients. Previous studies provided a number of risk factors: cardiac arrest due to VF, appropriate ICD interventions, syncope, nonsustained VT, ventricular dysfunction, male gender, compound and digenic mutations, young age at the time of diagnosis, inducibility at programmed ventricular stimulation, cardiac MR abnormalities, amount of electroanatomic scar, scar-related fractionated electrograms, extent of T-wave inversion across precordial and inferior leads, low QRS amplitude, QRS fragmentation and elevated serum testosterone levels in males, and decreased estradiol levels in females.[6,11-13,25,29,30,47,51,55,57,58] The prognostic role of electrophysiologic study in patients with ARVC is controversial. The results of a RV electroanatomic voltage mapping study showed that the arrhythmic risk is related to the extent of RV scar lesions.[59] A recent study with a long-term (8.5 years) follow-up of 116 desmosomal gene mutation carriers with no prior sustained VT or VF showed that the arrhythmic risk during the follow-up is strongly related to the ARVC phenotype expression and presence of major risk factors such as syncope, ventricular dysfunction, or nonsustained VT and most of sustained arrhythmic events occurred in patients with overt disease and major risk factors.[60] Another large Italian study showed that among 301 patients with ARVC, atrial fibrillation, syncope, participation in strenuous exercise after the diagnosis, hemodynamically tolerated sustained monomorphic VT, and a male gender were risk factors for life-threatening arrhythmic events during the follow-up.[23]

Many studies with a genetic analysis showed that multiple or complex gene mutations were independent predictors of lifetime arrhythmic events or SCD, earlier occurrence of sustained VT/VF, more frequent LV dysfunction, heart failure, and cardiac transplantations.[11-13,25,42] However, no positive correlation was noted between the number of mutations and adverse outcome in a recent Japanese study.[28] These studies support the use of genetic testing as a prognostic impact, as the severity of the disease appears different according to the underlying gene or the presence of multiple mutations. However, a variable clinical expression among the same mutation carriers or even among family members suggests an effect of modifiers such as strenuous exercise. The North American Registry data showed that patients engaged in competitive exercise had an earlier presentation and higher risk of life-threatening arrhythmias and death when compared with inactive patients and those practicing only recreational sports.[61] A family history of SCD does not suggest an adverse prognosis in ARVC, suggesting a limited value of the genetic analysis in the risk stratification.[62]

7 | TREATMENT

The primary aim of the management of patients is the prevention of SCD and improving the quality of life by reducing arrhythmic and heart failure symptoms.[37] Therapeutic options consist of lifestyle modifications, pharmacological treatment, catheter ablation, ICDs, and heart transplantations.[6] As ARVC is a progressive disease changes in the therapeutic strategy may be needed during the follow-up.

7.1 | Lifestyle modification

Avoidance of competitive and strenuous sports is recommended in patients with ARVC. Endurance exercise has been shown to accelerate the progression of disease in both humans and animal models.[63-67] Physical exercise may aggravate mechanical uncoupling of myocytes. Impaired cell-to-cell adhesion may promote myocyte death during competitive sports activity-induced mechanical stress, which may trigger malignant ventricular arrhythmias.[37] Physical exercise increases wall stress to a greater extent in the RV than in the LV.[68]

About one-third of patients in North American Registry were athletes.[69] ARVC carriers who were endurance athletes and were symptomatic at a younger age, have more advanced disease, and experience more heart failure and arrhythmic events than those that are nonathletic.[66] Among the PKP2 mutation carriers, those who developed VT/VF were endurance athletics and that had higher intensity exercise during adolescence were associated with adverse outcomes.[67] Recent Japanese study also showed that competitive sports activity was associated with occurrence of lethal ventricular arrhythmias among young victims.[28] As competitive sports activity has been shown to increase the risk of SCD by fivefold in adolescent and young adults with ARVC,[70] early identification of affected athletes by preparticipation screening from age 11 and 12 years may life-saving.[23,71,72]

Previous studies suggested that restricting unaffected desmosomal mutation carriers from endurance and high-intensity exercise is recommended but potentially not from the AHA-recommended minimum levels of exercise (≤650 MET hour/y) for healthy adults.[67]

7.2 | Medical therapy

Antiarrhythmic drugs are used in patients with ARVC to improve the quality of life by preventing symptomatic ventricular and atrial

arrhythmias. Usual medication consist of β-blockers, amiodarone, and sotalol.[7,23,69,73,74] Although some studies showed beneficial effects of sotalol and amiodarone, most studies suggested no significant effects of those drugs in reducing the rate of life-threatening arrhythmic events.[13,23,56,69,73-75] Despite those limited data, β-blockers are currently recommended for both prevention of arrhythmias and reduction in ventricular wall stress. One recent study showed combination of sotalol/metoprolol and flecainide may be another option in refractory VT.[76] For patients with heart failure, standard pharmacological treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and diuretics is recommended. Long-term oral anticoagulation is generally indicated for secondary prevention in patients with documented thromboembolisms.[6] A low birthweight of a newborn was associated with β-blocker therapy during pregnancy.[32]

7.3 | Catheter ablation

Catheter ablation is a therapeutic option for patients with sustained monomorphic VT. Although no significant reduction in life-threatening arrhythmic events during the follow-up was observed, catheter ablation results in symptomatic improvement by a significant reduction in the burden of VT.[23,75,77] Additional antiarrhythmic drug therapy, repeated ablation, and backup ICD implantations are required to provide suppression of VTs and SCD prevention.[6]

The use of 3D electroanatomic mapping systems and epicardial ablation are associated with a somewhat better outcome. However, the risks of major complications associated with epicardial ablation are considerable.[77] Another aggressive study with endocardial ablation, adjuvant epicardial ablation, and substrate modification had an excellent long-term arrhythmia-free survival rate of 71% with a mean follow-up of 56 ± 44 months.[74] However, these results are from highly experienced centers and the same results may not be attainable in most centers.

7.4 | ICD

ICD implantation is the only proven therapy for the prevention of SCD in patients with ARVC. The most important decision in patients with ARVC is whether to implant an ICD or not.[78] As the outcomes of ARVC studies are so diverse, recommendations on ICD therapy for primary prophylaxis are challenging.[7] Inducibility at electrophysiologic study and nonsustained VT are reported as independent strong predictors of an appropriate ICD therapy implanted for primary prevention.[78] Another recent study reported that 47% of the patients implanted for primary prevention of life-threatening arrhythmic events received an appropriate shock during 5.8 years of follow-up.[23] Their conclusion was that patients with risk factors such as a male gender, participation in strenuous exercise after the diagnosis, history of atrial fibrillation, syncope, and hemodynamically tolerated sustained monomorphic VT should be recommended for an ICD implantation.[23]

In a large (n = 610) meta-analysis with patients with ARVC who underwent ICD implantations for primary or secondary prevention of SCD, the annual rate of appropriate and inappropriate ICD intervention was 9.5% and 3.7%, respectively, during a mean follow-up of 3.8 years.[73] Patients with a history of an aborted SCD, poorly tolerated VT, and syncope have the greatest risk of SCD, and ICD therapy is recommended in this group. This meta-analysis revealed a low incidence of cardiac and noncardiac mortality after ICD implantations in patients with ARVC. However, it also showed that ICD-related complications are common and lead to considerable ICD-related morbidity.[73] Asymptomatic ARVC patients who underwent ICD implantations only because of a family history of SCD may not benefit from ICD therapy.

The proper sensing and pacing by the ICD may be difficult in diseased RV.[78,79] Therefore, particular attention should be paid to a progressive decrease in the R-wave sensing amplitude during the follow-up, which may compromise an adequate device function and may indicate a disease progression.[6] Two studies showed that 4% of patients required an additional septal lead owing to the malfunction of lead at the RV apex during mean follow-up of 3.3 and 4.7 years, respectively.[78,79] To prevent this complication, implantation of lead at RV septum is recommended (Figure 6).

A single-chamber ICD system is recommended to minimize the incidence of long-term lead-related complications especially in the young.[6] As, ATP is highly effective (92%) in terminating VT episodes in ARVC patients, all ICDs should be programmed for ATP and the conventional transvenous ICD is preferred.[57]

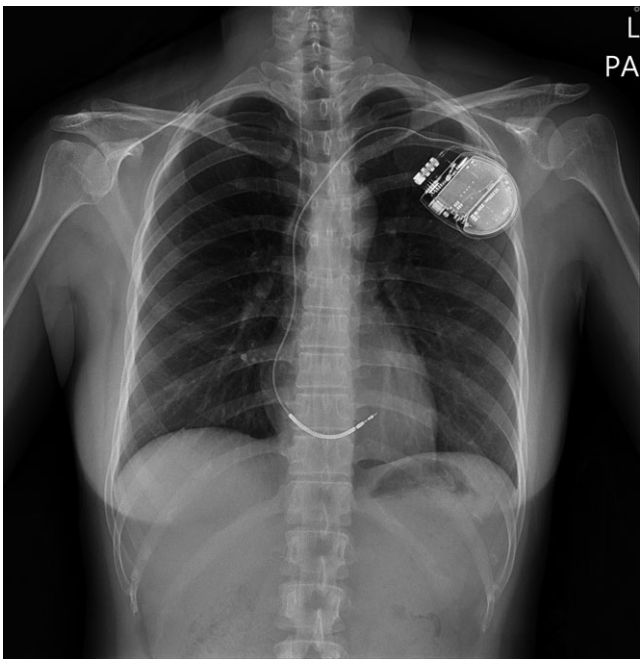

FIGURE 6 Thirty-year-old woman survived a cardiac arrest due to ventricular fibrillation. After a diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) was made, an implantable cardioverter defibrillator was implanted in the right ventricular septum to avoid sensing problems associated with fibrofatty infiltration in the right ventricular apex

7.5 | Heart transplantation

Heart transplantation is recommended as a final therapeutic option in ARVC patients with refractory heart failure or VT/VF. Data from Johns Hopkins Registry showed that the most common indication for cardiac transplantation was heart failure and the 1-year survival rate was excellent as 94%.[38]

8 | CONCLUSIONS

Arrhythmogenic right ventricular cardiomyopathy is a kind of cardiomyopathy characterized by ventricular arrhythmia, fibrofatty infiltrations, and the risk of SCD. The diagnosis of ARVC is challenging especially in the early phase. The management of patients consists of a symptom control of palpitations, and dyspnea, and a reduction in the risk of SCD. Patients with ARVC should be excluded from competitive and strenuous exercise. The most important thing in the management of patients with ARVC is the identification of patients who would benefit from an ICD implantation. Other treatment modalities such as antiarrhythmic therapy, heart failure management, and catheter ablation are helpful for symptom control in patients.

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CONFLICTS OF INTEREST

Authors declare no Conflict of Interests for this article.

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