WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Arrhythmogenic Right Ventricular Cardiomyopathy - Pathogenesis, Diagnosis and Treatment Modalities

Tarun Singh[1*], Manish Kumar Maity[1], Garima Malik[1], Omveer Singh[1], Mamta Naagar[1], Md Shamshir Alam[2], Priyanka Tanwar[3]

[1]Department of Pharmacy Practice, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university), Mullana-133207, Ambala, Haryana, India

[2]Department of Pharmacy Practice, College of Pharmacy, National University of Science and Technology, PO Box 620, Postal code 130, Bosher-Muscat, Sultanate of Oman

[3]Department of Pharmacology, Bhagvan Mahavir Institute of Medical Sciences, Sonipat-131030, Haryana, India

*Address for correspondence

Dr. Tarun Singh

MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana - 133207, Ambala, Haryana, India

Email id- doctarunmmu@gmail.com

ABSTRACT

Fibro fatty infiltration of the myocardium, ventricular arrhythmias, and heart failure are all symptoms of arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is a common cause of syncope, sudden death, ventricular arrhythmias in children and adolescents. Recent advancements in diagnostic techniques will aid in the early detection and correct care of at risk individuals. In addition to medical therapy and catheter ablation of ventricular tachycardia, rigorous exercise restriction and the installation of implanted cardioverter defibrillators (I.C.D) are crucial. Recent genetic screening may aid in identifying asymptomatic carriers who are at risk of illness progression and death.

Keywords : Arrhythmia, Arrhythmogenic right ventricular cardiomyopathy, Cardiomyopathy, Heart failure

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a kind of cardiomyopathy marked by continuous fibrofatty replacement of the right ventricle (RV) and life-threatening ventricular arrhythmias with left bundle branch block (LBBB) structure [1, 2, 3, 4].

More individuals with ventricular arrhythmias are being identified as ARVC as diagnostic modalities such as 2D echocardiography, cardiac magnetic resonance (MR), and genetic testing become more widely available. Risk stratification, lifestyle modification, and family screening are all part of the care of such individuals, especially those who are asymptomatic. Because most doctors have little expertise managing patients with ARVC, making decisions can be difficult.

In around half of cases, arrhythmogenic right ventricular cardiomyopathy is a family condition that is passed down as an autosomal dominant characteristic with varying penetrance. In the general population, ARVC is predicted to affect 1 in 5000 people, however it is substantially higher in particular locations, such as Padua, Italy [3, 5, 6]. The real prevalence is difficult to quantify because of age dependent penetrance and varied expression. This disease varying frequency in different regions of the world might be attributed to disease clustering in certain geographic locations.

PATHOGENESIS

- **Genetic Background**

The illness in the desmosome causes arrhythmogenic right ventricular cardiomyopathy. Desmosomes are present in the skin and myocardium, and they play a role in cell mechanical attachment as well as intracellular and intercellular signal transmission. Plakoglobin, plakophilins, desmoplakin, desmogleins, and desmocollins make up desmosomes [3]. Plakoglobin (JUP), desmoplakin (DSP), plakophilin2 (PKP2), desmoglein2 (DSG2), and desmocollin2 (DSG2) are the most common desmosomal proteins that induce ARVC (DSC2) [7, 8]. Nondesmosomal gene mutations cause a small percentage of instances.

The intercellular connection is broken by aberrant desmosomes, especially when mechanical stress is present. In the pathophysiology of ARVC, the canonical Wntcatenin signalling pathway is also implicated. By reducing the expression of adipogenic and fibrogenic genes, catenin interacts with

members of the TCFLET (Tcell factor–lymphocyte enhancing factor) family of transcriptional factors and prevents the development of mesodermal precursors into adipocytes and fibrocytes [9]. Plakoglobin is translocated from the sarcolemma to the nucleus after aberrant desmosomal formation, counteracting the actions of catenin. Plakoglobin therefore inhibits Wntcatenin signalling while increasing adipogenic and fibrogenic gene expression. After then, the normal fibrofatty alterations appear [10].

Arrhythmogenic right ventricular cardiomyopathy is primarily passed down through the generations as an autosomal dominant characteristic. Carvajal syndrome and Naxos disease are two cardiocutaneous disorders that have autosomal recessive variants [8]. Compound and digenic heterozygosity were shown to be widespread in several research, and these numerous mutations were linked to earlier manifestation and a more malignant phenotype, implying "digenic heterozygosity" [11, 12, 13]. A recent animal study found that deletion of PKP2 in adult myocytes was enough to cause an arrhythmia without overt structural illness, which then progressed to an ARVC and eventually, biventricular dilated cardiomyopathy (DCM) [14].

- **Pathology**

The key observations in ARVC are progressive cardiac cell loss and consequent fibrofatty infiltration. Fibrofatty infiltration begins in the epicardium, progresses to the endocardium, and results in wall weakening and aneurysmal alterations, particularly in the RV inlet, RV outlet, and apex [1, 2, 15]. With the discovery of a high incidence of left ventricular (LV) involvement, this paradigm has recently modified [13, 15, 16, 17, 18, 19]. Electrical conduction is slowed by the fibrofatty infiltration, and ventricular tachyarrhythmias may ensue. According to a recent study, fibrosis develops after mechanical failure is discovered, implying that the fibrosis is reparative [14].

Initially, arrhythmogenic right ventricular cardiomyopathy was thought to be a dysplasia of the RV myocardial, a developmental abnormality [1]. ARVC, on the other hand, is currently thought to be a hereditary cardiomyopathy [15]. Inflammatory infiltrations are linked to fibrofatty infiltrations in some individuals [6, 15, 20, 21].

The start of ARVC in teenagers might be linked to the completion of intercalated disc maturation or the requirement for a particular level of activity before the illness manifests [4]. In the natural history of ARVC, certain phases have been proposed. A structural change is nonexistent or minimal in the early "concealed phase," but patients may be at risk of SCD due to persistent VT or ventricular fibrillation (VF), which is comparable to ion channel dysfunction [3, 14, 22, 23]. Cerrone et al. [24] suggested that fibrofatty changes could be preceded by gap junction remodelling, which is associated with a reduction in the amplitude of the sodium current, slowed conduction, and an increased propensity for ventricular arrhythmias, and that these changes could occur in the absence of detectable structural disease, similar to the ARVC concealed phase. Brugada syndrome phenotype might be caused by a PKP2 mutation that causes inadequate sodium current [22]. The majority of SCDs happen in the course of normal daily activity [16, 20].

Patients with ventricular arrhythmias and apparent structural abnormalities of the ventricles are in the overt "electric phase." Patients with the early hidden phase may experience VT, although they have a decreased chance of SCD. In a large transatlantic investigation, individuals with monomorphic VT had a median age of 36 years, which was 13 years higher than those with SCD [25].

Heart failure, ventricular arrhythmias, and thromboembolisms are common in the latter stages. A recent research found that around one-fifth of their patients presented beyond the age of 50 years, and that they were less likely to have antecedent syncope, ECG abnormalities, ventricular ectopy, or detectable pathogenic mutations, and that they had more atrial arrhythmias than patients who presented earlier [26].

CLINICAL PRESENTATION

From exercise-related SCD as a first symptom in the young to biventricular heart failure in the elderly, the clinical presentation is varied. The majority of ARVC patients seek medical help due to ventricular arrhythmias and ECG abnormalities. Even among members of the same family or individuals bearing the same mutation, the disease's manifestation varies greatly. The majority of ARVC cases are familial with autosomal dominant inheritance, imperfect penetrance, and variable expressivity. This shows that environmental variables and other genetic modifiers, such as age, sex hormone changes, differences in the quantity and intensity of intense activity, and the existence of additional modifier genes, have a role in the expression of ARVC.

SCD is commonly caused by arrhythmogenic right ventricular cardiomyopathy, which is more common in young individuals [16, 20]. Palpitation, syncope, VT, and SCD are common clinical symptoms that appear between the second and fourth decades of life [4, 17, 25]. Between the ages of 21 – 40 years, the risk of life-threatening arrhythmias peaks at 4.0 per 100 person-years [23]. Male mutation carriers with a childhood onset were more likely to present with SCD or an aborted cardiac arrest, whereas adults were more likely to present with prolonged VT [27]. Radical mutant carriers displayed quicker onset of deadly ventricular arrhythmias than mis-sense mutation carriers or mutation-negative individuals, according to a recent Japanese study [28]. Men have a higher prevalence, earlier onset, and more malignant arrhythmic expression than women, which can be explained by the effect of sex hormones and variations in exercise volume and intensity [6, 25, 29, 30]. A previous study found no significant differences between men and women when it came to the prevalence of heart failure and LV dysfunction [25]. Females, on the other hand, had a much greater chance of heart failure mortality or heart transplantation, according to a recent Japanese study [29]. The lack of family members, longer follow-up, and smaller body surface area of patients in the Japanese research explained the disparities [29].

On physical examination, at least half of the patients show normal results [1]. A tricuspid regurgitation murmur and a huge a wave may be heard when the RV dilates. A normal ECG is found in about one-third to half of ARVC patients. More than half of patients develop RV related ventricular arrhythmias, and these ventricular arrhythmias often have various QRS morphologies [7]. T wave inversion in V1 to V3 is the most prevalent repolarization problem. Epsilon waves can be found in the right precordial leads but only a small percentage of individuals have ECG and clinical signs of Brugada syndrome [31]. Some unexpected perioperative fatalities appear to be caused by arrhythmogenic right ventricular cardiomyopathy [20]. The majority of pregnancies were also well tolerated [32]. According to one autopsy investigation, 2 out of 200 occurrences of SCD linked to ARVC occurred after delivery [20].

Patients with ARVC are more likely to develop atrial arrhythmias, and they do so at a younger age than the general population [23, 33]. Atrial

arrhythmias are clinically significant since they are linked to unnecessary ICD shocks and a higher risk of SCDs and heart failure. A recent study found that LV involvement differed by age and was more common in patients with advanced stages of the disease [2]. With the use of cardiac MR, biventricular or left dominant variants may now be seen at any stage of the illness [18, 19, 34]. Some believe that the term "arrhythmogenic cardiomyopathy" should be used instead of ARVC [34]. A left dominant variant of ARVC is seen in a small percentage of patients. Right bundle branch block (RBBB) type ventricular arrhythmias, T wave inversion in the inferior or lateral leads, and LV dysfunction define the left dominant variant [34]. Individuals with DSP and DSG2 mutations are more likely to have a left dominant form than patients with PKP2 mutations [12, 13, 19, 25]. According to one Chinese study, LV involvement might indicate a nonsense desmosomal gene mutation [17].

DIAGNOSIS

In all young individuals with syncope, VT, or cardiac arrest, arrhythmogenic right ventricular cardiomyopathy should be considered. In 1994, the International Task Force Criteria were created, which were based on structural, histologic, ECG, arrhythmic, and familial traits [35]. Regrettably, this criterion was insensitive to early and familial illness [35]. The clinical diagnostic criteria were changed in 2010 in order to increase diagnostic sensitivity while retaining specificity [36]. The revised criteria incorporated qualitative as well as quantitative data, as well as novel diagnostic methods such as cardiac magnetic resonance imaging and genetic testing. Even with updated criteria, however, the diagnosis is still difficult [37]. Regrettably, the new criteria exclude a left dominant form and are unable to distinguish sarcoidosis from ARVC [34, 38, 39].

- **Genetic test**

A significant diagnostic criteria for individuals with suspected ARVC is the discovery of a potential gene mutation. In up to 60% of patients, gene alterations are discovered [4, 13, 17, 25, 28, 42, 48]. As a result, the absence of an identified mutation does not rule out ARVC as a diagnosis. PKP2 is the most usually impacted gene, followed by DSP, DSG2, JUP, and DSC2, while screening of nondesmosomal genes has a minor impact on the incidence of mutation identification [4, 12, 17, 37, 42, 49]. In Caucasian and Chinese research, the PKP2 mutation is the most prevalent desmosomal gene mutation [4, 12, 17, 42]. However, a recent Japanese study found that the DSG2 mutation is the most frequent, suggesting that there is considerable racial variation even among Asians [28].

The study finds variations of unknown relevance in another 16% of the cases. The signal-to-noise ratio is roughly 4:1, which is substantially lower than in long QT syndrome (19:1) or catecholaminergic polymorphic VT (20:1) [8]. While radical mutations are more likely to result in ARVC alterations, uncommon missense mutations should be regarded with caution because the incidence of missense mutations was equal in probands and controls [49]. Mis-sense mutations in Caucasian patients with a conserved PKP2 and DSG2 residue and inside the DSP and DSG2 "hot zone" are more likely to be pathogenic [49]. According to a recent Japanese study, DSG2 mutations are generally often missense, but PKP2 mutations are almost always radical [28]. Some "genetic variations of undetermined significance" mutations may function as modifiers.

When it comes to getting a DNA test and interpreting its results, extreme caution is required. Rather of ordering the genetic test, some specialists advise referring a patient with a doubtful ARVC diagnosis to a speciality institution [8]. The absence of a mutation in the context of convincing clinical evidence should not bring the diagnosis into doubt, nor should the existence of a mutation overrule the clinical judgement about the diagnosis of ARVC [49].

- **Cardiac MR**

Cardiac MR has become the standard imaging approach because it allows for the early detection of both structural and functional ventricular issues using late gadolinium enhancement, even before wall thinning or motion abnormalities arise [18, 37, 50]. Unfortunately, the updated criteria do not incorporate late gadolinium enhancement. The combined evaluation of wall motion abnormality with signal abnormality including fat infiltration and late gadolinium enhancement achieved high diagnostic accuracy, according to a recent Swiss study. 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]. In ARVC mutation carriers, electrical abnormalities on the ECG and Holter monitoring are known to occur before observable structural problems [51]. In the absence of these electrical anomalies, cardiac MR is probably unnecessary.

Patients with claustrophobia, unstable arrhythmias, and some implanted cardiac devices cannot undergo cardiac MR. It is difficult to tell the difference between ARVC and cardiac sarcoidosis and myocarditis using cardiac MR. Some experts believe that cardiac MR should only be used routinely in facilities with skilled specialists.

DIFFERENTIAL DIAGNOSIS

In certain circumstances, distinguishing this condition from other disorders might be difficult. It is difficult to tell the difference between early-phase ARVC and RV outflow tract (RVOT) tachycardia or ectopy [52, 53]. LBBB with inferior axis is the most common morphology in individuals with idiopathic RVOT tachycardia. Patients with ARVC, on the other hand, may have a variety of VT morphologies, the most common of which are LBBB with a superior axis. When compared to RVOT tachycardia patients, early phase ARVC patients showed somewhat poorer RV function, more severe RV mechanical dispersion, and a larger RV diameter [53]. RVOT tachycardia or ectopy with a QRS duration in lead I of 120 ms, the earliest onset QRS in lead V1, QRS notching, and a transition of V5 or later were all shown to indicate the occurrence of ARVC in one research [54]. RVOT ectopy with an intrinsicoid deflection time >80 ms, a QS pattern in lead V1, and a QRS axis >90° was shown to be related with early ARVC in a recent research [52]. Symptoms of Brugada syndrome may be present in certain people [31]. Sarcoidosis, myocarditis, congenital anomalies, pulmonary hypertension, RV infarct, and DCM are among the other differential diagnosis. In cases with elderly onset, nonfamilial pattern, high-grade atrioventricular block, and

mediastinal lymphadenopathy, sarcoidosis should be suspected [39].

- **Prognosis**

Because ARVC is a progressive illness, risk factors may alter over time, necessitating reevaluation of the risks on a regular basis. The key components of overall mortality in such individuals are heart failure and SCD [29, 55, 56]. During a median follow-up of 7 years, 72 % of index patients who presented alive had persistent ventricular arrhythmias, according to a large (n = 1001) transatlantic research [4]. SCD occurred more commonly in patients without an ICD during follow-up, and ARVC development culminating in symptomatic heart failure was seen in 13% of patients. Overall, cardiac mortality and the need for cardiac transplants were both modest, at 6% and 4% respectively. At the latest follow-up, 89 % of the patients were still alive. As a result, if detected and treated promptly, the long-term outcome was excellent. During the follow-up period, ICD implantations dramatically decreased the incidence of SCD and improved the long-term result. The illness course and prognosis were similar in index patients with and without detected mutations; however the disease start was earlier in the index individuals with mutations. The presence of mutations and the presence of symptoms during the initial examination had a detrimental impact on the long-term prognosis of the family members. A recent Japanese research found that family members seldom suffered ARVC-related symptoms [28], while another Japanese study found that heart failure was the leading cause of death (84 %) [56]. The increased rate of heart failure-related mortality might be attributable to intensive therapeutic therapy, such as ICD placement.

Different studies have shown a wide range of yearly death rates. Reports from tertiary referral centers with high-risk patients overstated the dismal prognosis of ARVC patients, while research using community-based patient cohorts and screening of familial ARVC indicated a substantially better prognosis.

According to the previously stated big transatlantic investigation, the majority of family members (82%) was asymptomatic and had a superior event-free survival rate than the index patients [4]. Symptoms at first evaluation and the existence of mutations had a significant impact on long-term results in family members; family members with mutations had worse clinical outcomes [4].

- ❖ **Risk Stratification**

The electrical stability and ventricular performance of individuals with ARVC have a big impact on their prognosis. To properly comprehend the phenotype of patients, researchers must first grasp the involvement of both genetic background and environmental modifiers. Previous research identified a number of risk factors, including cardiac arrest due to VF, appropriate ICD interventions, syncope, nonsustained VT, ventricular dysfunction, male gender, compound and digenic mutations, young age at 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, and low QRS amplitude , QRS fragmentation and elevated serum testosterone levels in males, and decreased estradiol levels in females [6, 11, 12, 13, 25, 29, 30, 47, 51, 55, 57, 58]. Electrophysiologic studies' prognostic value in patients with ARVC is debatable. The degree of RV scar lesions is connected to the arrhythmic risk, according to the findings of an RV electro-anatomic voltage mapping research [59]. A recent study of 116 desmosomal gene mutation carriers with no prior sustained VT or VF found that arrhythmic risk during follow-up is strongly related to ARVC phenotype expression and the presence of major risk factors such as syncope, ventricular dysfunction, or nonsustained VT, and that the majority of sustained arrhythmic events occur in patients with overt disease and major risk factors [60]. Another large Italian study found that atrial fibrillation, syncope, intense activity after diagnosis, hemodynamically tolerated persistent monomorphic VT and male gender were all risk factors for life-threatening arrhythmic events during follow-up in 301 patients with ARVC [23].

Multiple or complex gene mutations were found to be independent predictors of lifetime arrhythmic episodes or SCD, earlier onset of prolonged VT/VF, more frequent LV dysfunction, heart failure, and cardiac transplantation in many investigations using genetic analysis [11, 12, 13, 25, 42]. In a recent Japanese study, however, no link was found between the number of mutations and poor outcomes [28]. The severity of the disease appears to change depending on the underlying gene or the existence of numerous mutations, according to these studies, which support the use of genetic testing as a prognostic factor. Variable clinical manifestation among the same mutation carriers or even among family members, on the other hand, shows a role for modifiers like vigorous activity. When compared to sedentary patients and those who simply participated in leisure sports, the North American Registry data revealed that competitive athletes presented earlier and had a greater risk of life-threatening arrhythmias and death [61]. A family history of SCD did not predict a poor outcome in ARVC, indicating that genetic analysis has little utility in risk stratification [62].

TREATMENT MODALITIES

The main goal of patient care is to avoid SCD and improve quality of life by minimising arrhythmic and heart failure symptoms [37]. Lifestyle changes, pharmaceutical therapy, catheter ablation, ICDs, and heart transplants are all alternatives for treatment [6]. Because ARVC is a progressive condition, it is possible that adjustments in the treatment strategy will be required throughout follow-up.

- **Lifestyle Modification**

In patients with ARVC, competitive and intense sports should be avoided. In both people and animal models, endurance exercise has been demonstrated to hasten the course of illness [63, 64, 65, 66, 67]. Mechanical uncoupling of myocytes can be aggravated by physical activity. Impaired cell-to-cell adhesion may enhance myocyte mortality during mechanical stress generated by competitive sports activities, which can lead to malignant ventricular arrhythmias [37]. Physical activity raises wall tension in the RV more than it does in the LV [68].

Athletes made up around a third of the patients in the North American Registry [69]. ARVC carriers who were endurance athletes and become symptomatic at a younger age have more severe disease and are more likely to have cardiac failure and arrhythmic events than nonathletic ARVC carriers [66]. Those with the PKP2 mutation who acquired VT/VF were endurance athletes and had greater intensity activity throughout adolescence, which were linked to negative outcomes [67]. A recent Japanese study also found a link between competitive sports and the prevalence of deadly

ventricular arrhythmias in young patients [28].

Because competitive sports have been proven to raise the risk of SCD in adolescent and young adults with ARVC by fivefold, [70] early identification of afflicted athletes by pre-participation screening starting at the age of 11 and 12 years may be lifesaving [23, 71, 72].

Previous research has shown that unaffected desmosomal mutation carriers should avoid endurance and high-intensity exercise, but not the AHA's recommended minimum levels of exercise for healthy individuals (≤650 MET hour/y) [67].

- **Medical Therapy**

In individuals with ARVC, antiarrhythmic medicines are used to improve quality of life by reducing symptomatic ventricular and atrial arrhythmias. Blockers, amiodarone, and sotalol are common medications [7, 23, 69, 73, 74].

Although some researches have shown that sotalol and amiodarone have favourable benefits, the majority of investigations have found that they had no meaningful effect on the rate of life-threatening arrhythmic events [13, 23, 56, 69, 73, 74, 75].

Despite the lack of evidence, blockers are currently suggested for both arrhythmia prevention and ventricular wall stress reduction. In refractory VT, a combination of sotalol/metoprolol and flecainide was found to be an effective treatment choice in a recent trial [76]. Standard pharmacological therapy with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, blockers, and diuretics is advised for individuals with heart failure. In individuals with proven thromboembolisms, long-term oral anticoagulation is usually recommended as a secondary preventative measure [6]. Beta Blocker treatment during pregnancy was linked to a newborn's low birthweight [32].

- **Catheter Ablation**

Catheter ablation is a treatment option for people with monomorphic VT that persists. Despite the fact that there was no substantial reduction in life-threatening arrhythmic events throughout the follow-up, catheter ablation results in symptomatic relief due to a large reduction in the burden of VT [23, 75, 77]. To suppress VTs and avoid SCD, further antiarrhythmic medication therapy, recurrent ablation, and backup ICD implantations are necessary [6].

A somewhat improved outcome has been linked to the use of 3D electroanatomic mapping equipment and epicardial ablation. The chances of serious problems associated with epicardial ablation, on the other hand, are significant [77]. With a mean follow-up of 56 ± 44 months, another aggressive research with endocardial ablation, adjuvant epicardial ablation, and substrate alteration showed an outstanding long-term arrhythmia-free survival rate of 71% [74]. These results, however, are from highly experienced centres, and they may not be replicated in most centres.

- **Implantable Cardioverter Defibrillator (ICD)**

The only established treatment for preventing SCD in people with ARVC is the implantation of an ICD. The most crucial choice for people with ARVC is whether or not to implant an ICD [78]. Because the results of ARVC research are so varied, making recommendations for ICD treatment for primary prophylaxis is difficult [7]. Inducibility during an electrophysiologic examination and nonsustained VT has been identified as independent strong predictors of a primary preventive ICD implant [78].

Another recent study found that after 5.8 years of follow-up, 47 percent of patients implanted for primary prevention of life-threatening arrhythmic episodes got an adequate shock [23]. Patients with risk factors such male gender, intense activity after diagnosis, history of atrial fibrillation, syncope, and hemodynamically tolerated persistent monomorphic VT should be advised for ICD installation, according to their findings [23].

During a mean follow-up of 3.8 years, the yearly rate of acceptable and inappropriate ICD intervention was 9.5 % and 3.7 %, respectively, in a large (n = 610) metaanalysis including patients with ARVC who received ICD implantations for primary or secondary prevention of SCD [73].

SCD is most likely in patients with a history of an aborted SCD, poorly tolerated VT, or syncope, and ICD treatment is indicated in this population. In patients with ARVC, this metaanalysis found a low rate of cardiac and noncardiac death following ICD implantation. However, ICD related problems are widespread and cause significant ICD morbidity [73]. Patients with asymptomatic ARVC who have ICDs implanted only because to a family history of SCD may not benefit from ICD treatment.

In a sick RV, adequate sensing and pacing by the ICD may be challenging [78, 79]. As a result, a progressive decline in the R wave sensing amplitude during the follow-up should be closely monitored, as this might jeopardise device operation and signal illness progression [6]. During a mean follow-up of 3.3 and 4.7 years, two studies revealed that 4% of patients required an extra septal lead due to lead dysfunction at the RV apex [78, 79]. The insertion of a lead at the RV septum is indicated to avoid this problem.

To reduce the risk of long-term lead-related problems, especially in children, a single-chamber ICD system is advised [6]. Because ATP is so successful at stopping VT episodes in ARVC patients (92 percent), all ICDs should be configured for ATP, and the traditional transvenous ICD should be used [57].

- **Heart Transplantation**

In ARVC patients with refractory heart failure or VT/VF, heart transplantation is indicated as a last resort. According to the Johns Hopkins Registry, heart failure was the most prevalent reason for cardiac transplantation, with a 94 % one-year survival rate [38].

CONCLUSION

Arrhythmogenic right ventricular cardiomyopathy is a kind of cardiomyopathy marked by ventricular arrhythmia, fibrofatty infiltrations, and an increased risk of SCD. ARVC is difficult to diagnose, especially in the early stages. Patients are managed by symptom control for palpitations and dyspnea, as well as a reduction in the risk of SCD. Competitive and vigorous activity should be avoided by patients with ARVC. The selection of patients who would benefit from an ICD implantation is the most critical aspect of ARVC therapy. Anti-arrhythmic medication, heart failure management, and catheter ablation are some of the other therapeutic options available to patients.

REFERENCES

1. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. *Circulation*. 1982;65:384–98.
2. Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *J Am Coll Cardiol*. 1997;30:1512–20.
3. Basso C, Corrado D, Marcus FI, et al. Arrhythmogenic right ventricular cardiomyopathy. *Lancet*. 2009;373:1289–300.
4. Groeneweg JA, Bhonsale A, James CA, et al. Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet*. 2015;8:437–46.
5. Peters S, Trümmel M, Meyners W. Prevalence of right ventricular dysplasia-cardiomyopathy in a non-referral hospital. *Int J Cardiol*. 2004;97:499–501.
6. Corrado D, Wichter T, Link MS, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an International Task Force Consensus Statement. *Circulation*. 2015;132:441–53.
7. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). *Eur Heart J*. 2015;36:2793–867.
8. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;13:1077–109.
9. Asimaki A, Tandri H, Huang H, et al. A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med*. 2009;360:1075–84.
10. Garcia-Gras E, Lombardi R, Giocondo MJ, et al. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. *J Clin Invest*. 2006;116:2012–21.
11. Xu T, Yang Z, Vatta M, et al. Compound and digenic heterozygosity contributes to arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol*. 2010;55:587–97.
12. Fressart V, Duthoit G, Donal E, et al. Desmosomal gene analysis in arrhythmogenic right ventricular dysplasia/cardiomyopathy: spectrum of mutations and clinical impact in practice. *Europace*. 2010;12:861–8.
13. Rigato I, Bauce B, Rampazzo A, et al. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Genet*. 2013;6:533–42.
14. Cerrone M, Montnach J, Lin X, et al. Plakophilin-2 is required for transcription of genes that control calcium cycling and cardiac rhythm. *Nat Commun*. 2017;8:106 https://doi.org/10.1038/s41467-017-00127-0, in press.
15. Basso C, Thiene G, Corrado D, et al. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? *Circulation*. 1996;94:983–91.
16. Cho Y, Park T, Yang DH, et al. Arrhythmogenic right ventricular cardiomyopathy and sudden cardiac death in young Koreans. *Circ J*. 2003;67:925–8.
17. Zhou X, Chen M, Song H, et al. Comprehensive analysis of desmosomal gene mutations in Han Chinese patients with arrhythmogenic right ventricular cardiomyopathy. *Eur J Med Genet*. 2015;58:258–65.
18. Aquaro GD, Barison A, Todiere G, et al. Usefulness of Combined Functional Assessment by cardiac magnetic resonance and tissue characterization versus Task Force Criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol*. 2016;118:1730–6.
19. Castelletti S, Vischer AS, Syrris P, et al. Desmoplakin missense and non-missense mutations in arrhythmogenic right ventricular cardiomyopathy: genotype-phenotype correlation. *Int J Cardiol* 2017. 10.1016/j.ijcard.2017.05.018, in press.
20. Tabib A, Loire R, Chalabreysse L, et al. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. *Circulation*. 2003;108:3000–5.
21. Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, et al. Genetics of myocarditis in arrhythmogenic right ventricular dysplasia. *Heart Rhythm*. 2015;12:766–73.
22. Cerrone M, Lin X, Zhang M, et al. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. *Circulation*. 2014;129:1092–103.
23. Mazzanti A, Ng K, Faragli A, et al. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol*. 2016;68:2540–50.
24. Cerrone M, Noorman M, Lin X, et al. Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haploinsufficiency. *Cardiovasc Res*. 2012;95:460–8.
25. Bhonsale A, Groeneweg JA, James CA, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J*. 2015;36:847–55.
26. Bhonsale A, te Riele AS, Sawant AC, et al. Cardiac phenotype and long-term prognosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with late presentation. *Heart Rhythm*. 2017;14:883–91.
27. te Riele AS, James CA, Sawant AC, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy in the pediatric population. Clinical characterization and comparison with adult-onset disease. *JACC Clin Electrophysiol* 2015;1:551–60.
28. Wada Y, Ohno S, Aiba T, et al. Unique genetic background and outcome of non-Caucasian Japanese probands with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Mol Genet Genomic Med.* Accepted for publication.
29. Kimura Y, Noda T, Otsuka Y, et al. Potentially lethal ventricular ventricular arrhythmias and heart failure in arrhythmogenic right ventricular cardiomyopathy. What are the differences between men and women?. *JACC Clin Electrophysiol* 2016;2:546–55.
30. Akdis D, Saguner AM, Shah K, et al. Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell

derived cardiomyocyte-based model to clinical biomarkers of disease outcome. *Eur Heart J*. 2017;38:1498–508.
31. Kim H, Cho Y, Park Y, et al. Underlying cardiomyopathy in patients with ST-segment elevation in the right precordial leads. *Circ J*. 2006;70:719–25.
32. Hodes AR, Tichnell C, Te Riele AS, et al. Pregnancy course and outcomes in women with arrhythmogenic right ventricular cardiomyopathy. *Heart*. 2016;102:303–12.
33. Camm CF, James CA, Tichnell C, et al. Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Rhythm*. 2013;10:1661–8.
34. Sen-Chowdhry S, Syrris P, Prasad SK, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *J Am Coll Cardiol*. 2008;52:2175–87.
35. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J*. 1994;71:215–8.
36. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533–41.
37. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med*. 2017;376:1489–90.
38. Tedford RJ, James C, Judge DP, et al. Cardiac transplantation in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2012;59:289–90.
39. Philips B, Madhavan S, James CA, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy and cardiac sarcoidosis: distinguishing features when the diagnosis is unclear. *Circ Arrhythm Electrophysiol*. 2014;7:230–6.
40. Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. *Circulation*. 2004;110:1527–34.
41. Yoerger DM, Marcus F, Sherrill D, et al. Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: new insights from the multidisciplinary study of right ventricular dysplasia. *J Am Coll Cardiol*. 2005;45:860–5.
42. Bao J, Wang J, Yao Y, et al. Correlation of ventricular arrhythmias with genotype in arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Genet*. 2013;6:552–6.
43. Denis A, Sacher F, Derval N, et al. Diagnostic value of isoproterenol testing in arrhythmogenic right ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2014;7:590–7.
44. Basso C, Ronco F, Marcus F, et al. Quantitative assessment of endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy/dysplasia: an in vitro validation of diagnostic criteria. *Eur Heart J*. 2008;29:2760–71.
45. Paul M, Stypmann J, Gerss J, et al. Safety of endomyocardial biopsy in patients with arrhythmogenic right ventricular cardiomyopathy: a study analyzing 161 diagnostic procedures. *JACC Cardiovasc Interv*. 2011;4:1142–8.
46. Pieroni M, Dello Russo A, Marzo F, et al. High prevalence of myocarditis mimicking arrhythmogenic right ventricular cardiomyopathy differential diagnosis by electroanatomic mapping-guided endomyocardial biopsy. *J Am Coll Cardiol*. 2009;53:681–9.
47. Corrado D, Basso C, Leoni L, et al. Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation*. 2005;111:3042–50.
48. Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the management of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2007;50:1813–21.
49. Kapplinger JD, Landstrom AP, Salisbury BA, et al. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. *J Am Coll Cardiol*. 2011;57:2317–27.
50. Bauce B, Rampazzo A, Basso C, et al. Clinical phenotype and diagnosis of arrhythmogenic right ventricular cardiomyopathy in pediatric patients carrying desmosomal gene mutations. *Heart Rhythm*. 2011;8:1686–95.
51. te Riele AS, Bhonsale A, James CA, et al. Incremental value of cardiac magnetic resonance imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol*. 2013;62:1761–9.
52. Novak J, Zorzi A, Castelletti S, et al. Electrocardiographic differentiation of idiopathic right ventricular outflow tract ectopy from early arrhythmogenic right ventricular cardiomyopathy. *Europace*. 2017;19:622–8.
53. Saberniak J, Leren IS, Haland TF, et al. Comparison of patients with early-phase arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract ventricular tachycardia. *Eur Heart J Cardiovasc Imaging*. 2017;18:62–9.
54. Hoffmayer KS, Machado ON, Marcus GM, et al. Electrocardiographic comparison of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract tachycardia. *J Am Coll Cardiol*. 2011;58:831–8.
55. Hulot JS, Jouven X, Empana JP, et al. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation*. 2004;110:1879–84.
56. Kikuchi N, Yumino D, Shiga T, et al. Long-term prognostic role of the diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia. *JACC Clin Electrophysiol*. 2016;2:107–15.
57. Link MS, Laidlaw D, Polonsky B, et al. Ventricular arrhythmias in the North American multidisciplinary study of ARVC: predictors, characteristics, and treatment. *J Am Coll Cardiol*. 2014;64:119–25.
58. Brun F, Groeneweg JA, Gear K, et al. Risk stratification in arrhythmic right ventricular cardiomyopathy without implantable cardioverter defibrillators. *JACC Clin Electrophysiol*. 2016;2:558–64.
59. Migliore F, Zorzi A, Silvano M, et al. Prognostic value of endocardial voltage mapping in patients with arrhythmogenic right ventricular

cardiomyopathy/dysplasia. *Circ Arrhythm Electrophysiol*. 2013;6:167–76.

60. Zorzi A, Rigato I, Pilichou K, et al. Phenotypic expression is a prerequisite for malignant arrhythmic events and sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy. *Europace*. 2016;18:1086–94.

61. Ruwald AC, Marcus F, Estes NA 3rd, et al. Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. 2015;36:1735–43.

62. Sen-Chowdhry S, Syrris P, Pantazis A, et al. Mutational heterogeneity, modifier genes, and environmental influences contribute to phenotypic diversity of arrhythmogenic cardiomyopathy. *Circ Cardiovasc Genet*. 2010;3:323–30.

63. Corrado D, Migliore F, Basso C, et al. Exercise and the risk of sudden cardiac death. *Herz*. 2006;31:553–8.

64. Heidbüchel H, Hoogsteen J, Fagard R, et al. High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification. *Eur Heart J*. 2003;24:1473–80.

65. Kirchhof P, Fabritz L, Zwiener M, et al. Age and training dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. *Circulation*. 2006;114:1799–806.

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

67. Sawant AC, Te Riele AS, Tichnell C, et al. Safety of American Heart Association recommended minimum exercise for desmosomal mutation carriers. *Heart Rhythm*. 2016;13:199–207.

68. La Gerche A, Heidbüchel H, Burns AT, et al. Disproportionate exercise load and remodeling of the athlete's right ventricle. *Med Sci Sports Exerc*. 2011;43:974–81.

69. Marcus GM, Glidden DV, Polonsky B, et al. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. *J Am Coll Cardiol*. 2009;54:609–15.

70. Corrado D, Basso C, Rizzoli G, et al. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol*. 2003;42:1959–63.

71. Corrado D, Basso C, Pavei A, et al. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA*. 2006;296:1593–601.

72. Corrado D, Schmied C, Basso C, et al. Risk of sports: do we need a pre participation screening for competitive and leisure athletes? *Eur Heart J*. 2011;32:934–44.

73. Schinkel AF. Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications. *Circ Arrhythm Electrophysiol*. 2013;6:562–8.

74. Santangeli P, Zado ES, Supple GE, et al. Long term outcome with catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2015;8:1413–21.

75. Yin K, Ding L, Li Y, Hua W. Long term follow up of arrhythmogenic right ventricular cardiomyopathy patients with an implantable cardioverter defibrillator for prevention of sudden cardiac death. *Clin Cardiol*. 2017;40:216–21.

76. Ermakov S, Gerstenfeld EP, Svetlichnaya Y, Scheinman MM. Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm*. 2017;14:564–9.

77. Philips B, Madhavan S, James C, et al. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2012;5:499–505.

78. Bhonsale A, James CA, Tichnell C, et al. Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter defibrillator implantation for primary prevention. *J Am Coll Cardiol*. 2011;58:1485–96.

79. Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation*. 2003;108:3084–91.