Arrhythmogenic Right Ventricular Cardiomyopathy

14

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14.1 Case Report

A 54-year-old man with a long history of brief episodes of palpitations was referred by a spoke hospital to our cardiology department due to two episodes of hemodynamically tolerated wide complex tachycardia treated with amiodarone infusion. Two days before, the patient's complaint of palpitations occurred while he was running.

Medical History and Cardiovascular Risk Factors

- Cardiovascular risk factors: systemic arterial hypertension.
- Family history: one brother died for sudden cardiac death (SCD) at age 23.
- At age 23, episodes of exercise-induced palpitations, of variable duration (minutes up to 1 h).
- In 2002, one episode of wide complex tachycardia (left bundle branch block morphology and top axis at 200 bpm) resolved with precordial thump.
- In 2012, the patient was hospitalized in a spoke hospital for frequent non-sustained ventricular arrhythmias. An echocardiogram revealed normal left ventricle and moderate dilatation of right ventricle with hypokinesis in the mid- and apical segments. The coronary angiogram showed noncritical stenosis. He underwent cardiac magnetic resonance (MRI) that was not conclusive for arrhythmogenic right ventricular dysplasia. The patient was recommended to stop physical activity and was discharged on sotalol 80 mg t.i.d.
- Over 3 years, the patient was stable and asymptomatic and refused any further cardiologist follow-up.
- *Allergies:* none.

Medications

Sotalol 80 mg t.i.d

Vital Signs

- Temperature: 36.3 °C
- Heart rate: 60 bpm
- Arterial blood pressure: 130/70 mmHg

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- Respiratory rate: 17 breaths/min
- Oxygen saturation: 99 %

Physical Examination

- General appearance: well developed, well nourished, alert, and cooperative
- Lungs: clear to auscultation bilaterally
- Heart: regular rate and rhythm without murmurs, gallops, or rubs
- Extremities: no peripheral edema, cyanosis or pallor. Warm and well perfused
- Abdomen: Nontender, nondistended, normoactive bowel sounds throughout, no hepatosplenomegaly, and no bruits

Laboratory Tests

Tests were within normal limits (hemoglobin 14 g/dl, white blood cells 7,320/mmc, creatinine 0.88 mg/dl, potassium 4.3 mEq/l, sodium 140 mEq/l, magnesium 1.7 mg/dl).

Instrumental Examination

The patient underwent electrocardiogram (ECG) and echocardiogram to evaluate the right and left ventricle function.

Surface 12-lead ECG revealed sinus rhythm (heart rate 56 bpm), first-degree atrioventricular block, anterior fascicular block, incomplete right ventricular block, the characteristic epsilon waves in leads V1–V4, and also inverted T-waves in inferior lead and leads V2–V6, with slightly prolonged QT interval (corrected QT –QTc = 463 ms). The right bundle was very abnormal with fractionation throughout the right bundle in keeping with a cardiomyopathic process (Fig. 14.1).

Echocardiogram revealed right ventricular enlargement with hypokinesis in the mid- and apical segments and mild tricuspid regurgitation. Also, right outflow dilatation (23 mm/m^2) with normal systolic pulmonary pressure was observed. The left ventricle was mildly enlarged with an ejection fraction of 50 % without regional wall motion abnormalities.

In order to better evaluate the right ventricular size, motility, and ejection fraction, the patient underwent cardiac MRI that revealed right ventricular dilatation with wall thickening and moderate dyskinesia in the mid- and apical segments. Right ventricular ejection fraction was deeply reduced, nearly 35 %. Left ventricle was mildly dilated with normal ejection fraction (Fig. 14.2). Unfortunately, the patient refused gadolinium injection.

Clinical Course and Therapeutic Management

These imaging and clinical findings were strongly suggestive for ARVC.

According to the last AHA/ACC/ESC guidelines [1], taking into account the history of wide complex tachycardia suggestive for hemodynamically stable sustained VTs and severe right ventricle dysfunction, the patient was judged to be at moderate risk for SCD and underwent bicameral implantable cardioverter defibrillator (ICD) implant without major and minor complications. The decision to implant a bicameral ICD was based on the presence of first-degree AV block, anterior fascicular block, and incomplete right ventricular block, so the patient was judged to be at risk of developing high-degree AV block in the future. Sotalol was suspended and QTc interval became normal (440 ms). Therapy with a β-blocker was administered because of the recurrent sustained VTs. Also, a genetic test for ARVC-related mutations was performed.

On the 9th day, the patient was discharged on metoprolol tartrate 50 mg daily. Patient was advised to avoid competitive sport.

All the family members were recommended to undergo cardiologic visit, ECG and echocardiography evaluation, and eventually genetic screening once the mutation is identified in the patient.

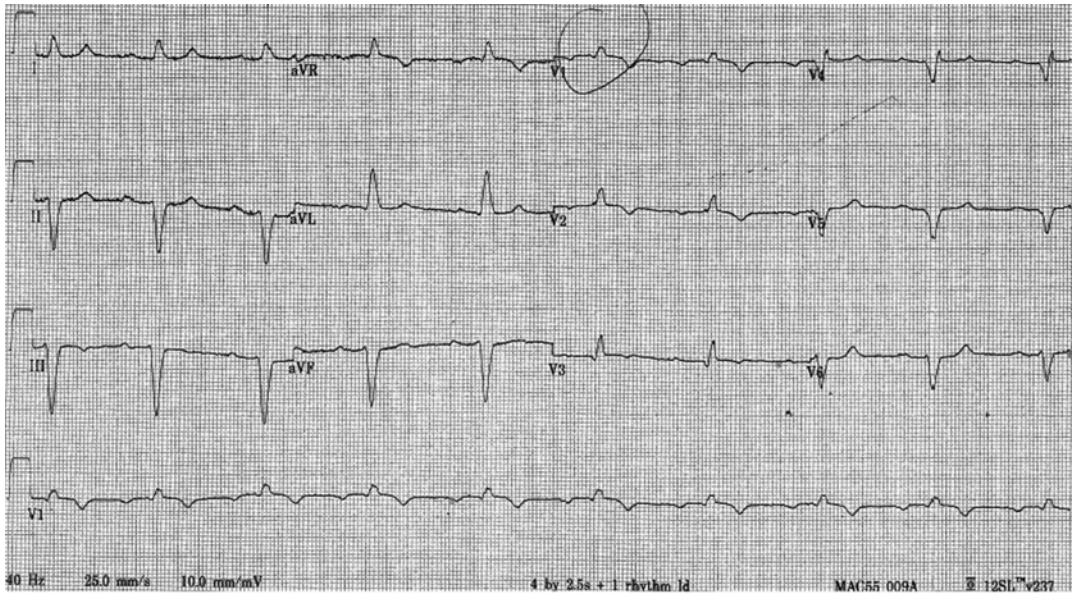

Fig. 14.1 ECG sinus rhythm (heart rate 56 bpm), first-degree atrioventricular block, anterior fascicular block, incomplete right ventricular block, characteristic epsilon waves in leads V1–V4, and also inverted T-waves in inferior lead and leads V2–V6, with prolonged QT interval (corrected QT–QTc = 463 ms). The right bundle is very abnormal with fractionation throughout the right bundle in keeping with a cardiomyopathic process

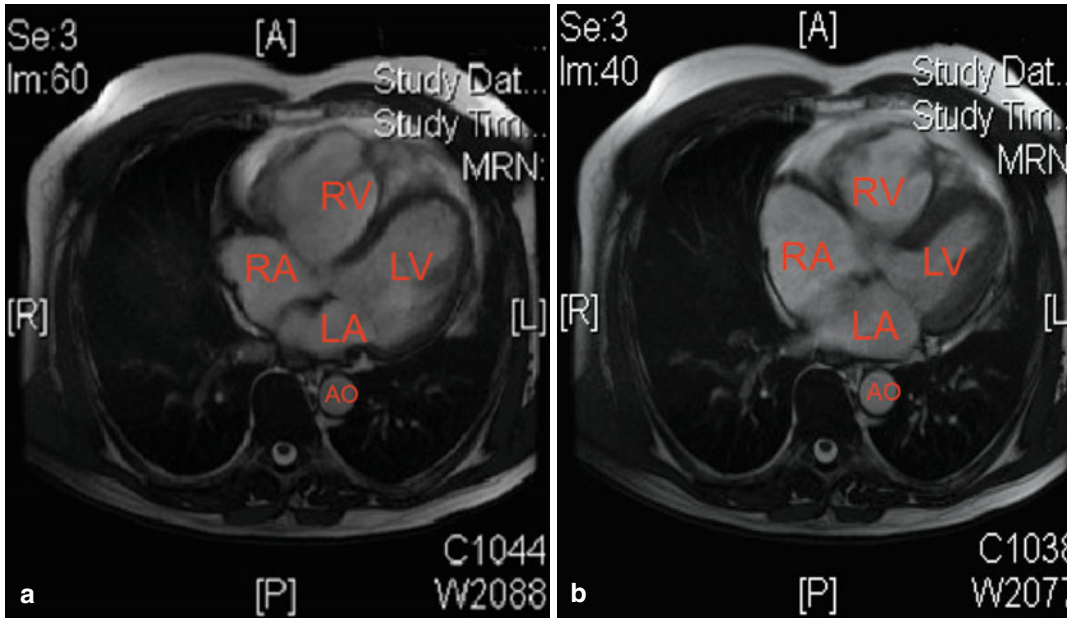

Fig. 14.2 Two axial FIESTA images (**a**, diastolic, and **b**, systolic) clearly depict a dilation of the four cardiac chambers, especially right ones. Wall of RV is prominently thinned

14.2 Arrhythmogenic Right Ventricular Cardiomyopathy

The arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as arrhythmogenic right ventricular dysplasia (ARVD), is a genetic disorder characterized clinically by malignant ventricular arrhythmias and an increased risk of sudden cardiac death (SCD), especially in young adults and athletes [2].

The ARVC is characterized by loss of myocytes and progressive fibroadipose replacement resulting in structural and functional changes of the right ventricle. However, considering the recent data showing a frequent involvement of the left ventricle, the ARVC is currently considered as a genetic disease of both ventricles and most properly called "arrhythmogenic cardiomyopathy" [2].

The adult prevalence in general population is about 1: 1,000–5,000 and is considered to be more common in individuals of Italian and Greek origin; however, the real prevalence in general population is likely to be underestimated [3].

Genetics

Data from genetic studies suggest that 30–50 % of cases are familial. The most common pattern of inheritance is an autosomal dominant form with incomplete penetrance and variable expressivity. The autosomal recessive inheritance form is less common and associated with cutaneous manifestations and wooly hair (Naxos disease, Carvajal syndrome).

To date, eight genes involved in the pathogenesis of CVAD have been identified; these genes encode for the desmosomal proteins [*JUP (plakoglobin), DSP (desmoplachina), Pkp2 (placofilina2), Gene (desmoglein-2), Dsc2 (desmocollina-2)*], the transforming growth factor (*TGF β3*), the transmembrane proteins (*TMEM43*), and the ryanodine receptor (*RYR2*)] [4].

Pathogenesis

The pathogenesis of ARVC is mostly related to reduced function of desmosomes which are intercellular adhesion complexes that provide mechanical connections between cardiac myocytes. In fact, it has been hypothesized that impaired cell adhesion may cause destruction and degeneration of cardiomyocytes, especially when subjected to mechanical stress (e.g., intense physical exercise) [2]. Because of the limited regeneration capacity of the myocardium, the repair process results in fibroadipose replacement which proceeds from the epicardium to endocardium. These process is completely absent at birth and likely begins during the puberty [2].

Anatomical fibrofatty replacement results in the free wall weakness and progressive ventricular dilatation with systolic dysfunction and aneurysm formation in the thinnest portions of the right ventricle, the so-called triangle of dysplasia (the apex, the inflow tract, and the outflow tract) [5]. Instead, fibrofatty replacement of the left ventricle generally involves the posterolateral wall, relatively thin, and rarely the interventricular septum [2].

Clinical Manifestations

The clinical presentation is more frequent between the second and the fourth decades. Because of genetic transmission with associated reduced penetrance, the severity of the clinical phenotype is somewhat variable.

In the natural history of ARVC, four stages are identified: (1) "concealed phase," characterized by the absence of symptoms and minor structural abnormalities (the SCD can be the first and the only manifestation of the disease); (2) "overt electrical instability," characterized by ventricular arrhythmias and morphofunctional cardiac abnormalities; (3) "right ventricular failure," with severe systolic dysfunction of the right ventricle

and initial or absent left ventricular abnormalities; and (4) "biventricular failure," with severe systolic dysfunction of both ventricles similar to a cardiomyopathy [2].

Ventricular/Supraventricular Tachyarrhythmias and Sudden Cardiac Death

VTs in patients with ARVC range from single extra beats to complex VT, symptomatic and not, and the frequency appears to be proportional to the severity of the disease. The most common VT is generally monomorphic with origin from the right ventricle and left bundle branch block morphology. The arrhythmic episodes may origin from the apex, the inflow tract, or the outflow tract; when the site of origin is the right outflow tract, a differential diagnosis with idiopathic VT is required [2].

Unfortunately, the SCD may be the first manifestation of the disease. The estimated mortality rate for SCD varies from 0.08 to 9 % per year [1].

Exercise, especially the endurance sport, is considered a precipitating factor for arrhythmias in patients with ARVC. This "trigger" effect is likely related to the increased right ventricular stimulation by catecholamine exposure; in addition, data from literature suggest that the exercise itself contributes to the right ventricle dilatation and consequently to the disease progression [2].

Supraventricular tachyarrhythmia (SVT), such as atrial fibrillation, atrial tachycardia, and atrial flutter, in association with ventricular arrhythmias, is present in up to 25 % of patients with ARVC; less commonly, SVT may be the only arrhythmia present [6].

Left Ventricular Involvement

The wider use of cardiac MRI has allowed to appreciate a more common involvement of the left ventricle in ARVC [7].

In a study of 200 patients undergoing MRI, three patterns of disease expression were identified:

- *Classic:* primarily affects the right ventricle and, only in advanced stages, the left ventricle (39 %).
- *Dominant left:* characterized by early and severe involvement of the left ventricle and relatively mild disease of the right ventricle. It is very insidious variant as fibroadipose replacement involves initially only the epicardium of the left ventricle without causing wall motion abnormalities. The use of MRI contrast medium allows the identification of nontransmural scar.
- *Biventricular:* characterized by a parallel involvement of both ventricles.

Diagnosis

The diagnosis of ARVC is complex and requires a high degree of clinical suspicion. To date, no single diagnostic test is enough sensitive and specific to confirm or rule out the disease; thus multiple parameters need to be considered.

The Task Force of the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology has developed the ARVC diagnostic criteria that take into account structural, histologic, arrhythmic, and genetic features. The original version of 1994 [8] that the revised version of 2010 [9] includes major and minor criteria collected in six main categories (Table 14.1). Based on this classification, definite diagnosis of ARVC requires two major criteria or one major and two minor or four minor criteria from different categories (Table 14.1).

In the suspicion of ARVC, as a general approach, it is recommended to go through a careful personal and family medical history, a 12-lead ECG, and a transthoracic echocardiography in all patients. Additional tests should be performed according to the clinical scenario or when the results of initial tests are not conclusive. Recommended tests are as follows:

Table 14.1 Task Force Criteria [9]

2010 Task Force Criteria Definite = 2 major or 1 major + 2 minor or 4 minor from different categories Borderline = 1 major + 1 minor or 3 minor Possible = 1 major or 2 minor	
1. Global/regional dysfunction/structural alterations	
Major	By 2D echo: Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32 mm (PLAX/BSA ≥19 mm/m^2) PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m^2) Fractional area change ≤33 % By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: RVEDV/BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) RV ejection fraction ≤40 % By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm
Minor	By 2D echo: Regional RV akinesia or dyskinesia and 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (PLAX/BSA ≥16 to <19 mm/m^2) PSAX RVOT ≥32 to <36 mm (PSAX/BSA ≥18 to <21 mm/m^2) Fractional area change >33 to ≤40 % By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RVEDV to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (fem) RV EF >40 to ≤45 %
2. Tissue characterization of wall	
Major	Residual myocytes <60 % by morphometric analysis (or <50 % if estimated), w/ fibrosis replacement of RV free wall myocardium in ≥1 sample, w/ or w/o fatty replacement of tissue on endomyocardial biopsy
Minor	Residual myocytes 60–75 % by morphometric analysis (or 50–60 % if est.) w/ fibrous replacement of the RV free wall in ≥1 sample, w/ or w/o fatty replacement of tissue on endomyocardial biopsy
3. Repolarization abnormalities	
Major	TWI (V1, V2, V3) or beyond; >14 years of age; in the absence of complete RBBB QRS ≥120 ms
Minor	TWI in V1 and V2; >14 years of age; in the absence of complete RBBB or in V4, V5, or V6 TWI in V1–V4; >14 years of age; in the presence of complete RBBB
4. Depolarization conduction abnormalities	
Major	Epsilon wave in right precordial leads (V1–V3)
Minor	Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on ECG: Filtered QRS duration (fQRS) ≥114 ms Duration of terminal QRS <40 μV ≥38 ms Root mean square voltage of terminal 40 ms ≤20 μV Terminal activation ≥55 ms measured from nadir of S-wave to end of QRS, including R′, in V1, V2, or V3, in the absence of complete RBBB
5. Arrhythmias	
Major	NSVT or sustained VT, LBBB morphology with superior axis
Minor	NSVT or sustained VT of RV outflow configuration, LBBB with inferior or of unknown axis >500 PVCs per 24 h on Holter monitoring
6. Family history	
Major	ARVC/D in first-degree relative who meets Task Force Criteria ARVC/D confirmed pathologically at autopsy or surgery in first-degree relative Identification of the pathogenic mutation (associated or probably associated w/ ARVC/D) in the patient under evaluation

(continued)

Table 4.1 (continued)

Minor	History of ARVC in first-degree relative in whom it is not possible to determine if the family member meets Task Force Criteria Premature SCD (<35 years of age) due to suspected ARVC/D in first-degree relative ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

RVOT right ventricular outflow tract, *PLAX* parasternal long axis, *PSAX* parasternal short axis, *BSA* body surface area, *RV* right ventricle, *RVEDV* right ventricle end-diastolic volume, *EF* ejection fraction, *TWI* T-wave inversion, *RBBB* right bundle branch block, *LBBB* left bundle branch block, *SAECG* signal-averaged electrocardiography, *NSVT* non-sustained ventricular tachycardia, *VT* ventricular tachycardia, *ARVC/D* arrhythmogenic ventricular cardiomyopathy/dysplasia, *SCD* sudden cardiac death, *PVC* premature ventricular complex

- Signal-averaged ECG (SAECG)
- 24 h ECG Holter
- Stress testing
- Cardiac MRI with gadolinium
- Right ventriculography
- Endomyocardial biopsy
- Electrophysiologic study and three-dimensional electroanatomic mapping
- Genetic testing

Electrocardiography (ECG)

In all patients with suspected diagnosis of ARVC, a 12-lead ECG is recommended. The sensitivity is suboptimal, because 40–50 % of patients have a normal ECG submission. However, reflecting the progressive nature of the disease, most patients develop characteristic ECG abnormalities years after the presentation, such as [10]:

- QRS prolongation, especially in lead V1 versus V6.
- Incomplete/complete right bundle branch block.
- Prolonged QRS terminal activation (≥55 ms measured from nadir of S-wave to end of QRS, including R′, in V1, V2, or V3, in the absence of complete RBBB).
- Epsilon waves in right precordial leads, particularly in V1 identified in 30 % of patients with ARVC. In order to detect epsilon waves and avoid ST distortion, ECG filters should be set with a low-frequency cutoff of 0.05 Hz and a high-frequency cutoff greater than 150 HZ in adults and 250 Hz in children.
- T-wave inversion in right precordial leads (V1, V2, V3) in the absence of complete right bundle branch block. This ECG feature, which can be a normal variant in children under 14 years of age, is present in 87 % of subjects with ARVC. The extension of the T-wave inversion also correlates with the degree of right ventricular dilatation and arrhythmic risk. T-wave inversion in leads V5–V6, instead, is an indirect sign of left ventricular involvement.

Late Potentials

Signal-averaged ECG abnormalities are common and have an excellent sensitivity and specificity for ARVC; however, they are not predictive of arrhythmic risk.

Late potential abnormalities are considered as minor criteria if they meet at least one of the following three conditions, without a QRS duration ≥110 ms [9]:

- Filtered QRS duration ≥114 ms
- Terminal QRS duration <40 microV and ≥38 Ms
- Root mean square voltage of terminal 40 ms ≤20 microV

Echocardiography

A transthoracic echocardiogram should be performed in all patients with the clinical suspicion

of ARVC. Echocardiography is a noninvasive method and readily available and easily allows right ventricle visualization in most patients. The echocardiographic findings frequently observed are [9]:

- Right ventricular dilation, especially the right outflow tract (RVOT)
- Reduction of right ventricular fractional area change
- Regional and global wall motion abnormalities of the right ventricle
- Morphological abnormalities of the right ventricle (trabecular derangement, hyperreflective moderator band, and aneurysms)

Left ventricular echocardiographic abnormalities are seen less frequently.

Cardiovascular Magnetic Resonance Imaging

In patients with suspected ARVC and no diagnostic results with other imaging modalities, cardiac MRI is strongly recommended. Cardiac MRI allows evaluation of right ventricle dilation, global and regional wall motion abnormalities, intramyocardial fat, focal wall thinning, and late gadolinium enhancement in fibrosis areas.

The main limitations of cardiac MRI are related to the limited experience of the centers and significant interobserver variability resulting in high rate of false positives. In addition, intramyocardial fat infiltration of the right ventricular wall should be interpreted with caution, as fat infiltration is frequently in healthy subjects, especially if elderly [2].

Right Ventriculography

Ventriculography may be useful to assess the structure and function of the right ventricle in patients with strong suspect for ARVC and nondiagnostic results with other imaging modalities. Regional right ventricle akinesia, dyskinesia, or aneurysms are generally observed [9]. However, since ventriculography is an invasive method, it is rarely used.

Electrophysiologic Testing and Electroanatomic Voltage Mapping

Electrophysiologic testing is of limited role in the diagnostic workup of patients with suspect ARVC. However, electrophysiologic testing has a role in the differential diagnosis between idiopathic outflow tract and the ARVC-related VT [11]. In fact, contrarily to VT in ARVC patients, the idiopathic outflow tract VT is not associated with ECG abnormalities, is more frequent in women, and is induced by isoprenaline infusion rather than programmed ventricular stimulation.

Electroanatomic voltage mapping is an innovative tool useful to identify and quantify areas of fibrosis by detection of low-voltage local right ventricle electrograms. Despite electroanatomic mapping increases accuracy in diagnosing, the technique is operator dependent, invasive, and costly.

Genetic Testing

The ARVC is a genetic disease and a desmosomal gene mutation identified in approximately 30–50 % of cases. However, given multiple mutations causing the disease and the variable penetrance, genetic testing should not be performed in all patients suspected for ARVC. Genetic tests are recommended for patients who meet the Task Force Criteria [9] for a definitive or borderline ARVC diagnosis and all first-degree relatives following the identification of the ARVC-causative mutation in an index case [12].

Endomyocardial Biopsy

Endomyocardial biopsy is an invasive procedure with poor sensitivity and specificity; thus, it is not recommended for the initial diagnostic workup.

When endomyocardial biopsy is performed, one major concern is related to the sampling error. The interventricular septum, which is the usual and low-risk biopsy site, is not generally useful in ARVC patients since it is not generally affected by the pathology. In addition, the istofibrofatty replacement cannot be considered a pathognomonic ARVC feature as it is also observed in healthy subjects, especially elderly. In the light of these data, in ARVC patients,

endomyocardial biopsy is a class IIb recommendation in the diagnostic workup for ARVC [13].

Differential Diagnosis for ARVC

- *Dilated cardiomyopathy*: biventricular dilated and congestive heart failure may be similar to ARVC with left ventricle involvement.
- *Uhl anomaly*: total lack of right ventricular myocardium. In ARVC, the myocardium is not completely absent but replaced by a variable degree of fibrosis.
- *Idiopathic VT*: Left bundle branch block morphology VT in a structurally healthy heart and absence of SCD familiarity.

Therapy and Prognosis

The therapeutic approach in ARVC patients is addressed to SCD prevention and relief of symptoms of arrhythmias related, as well as improvement in terms of functional capacity and survival in patients who develop heart failure. To achieve these goals, available treatment options include lifestyle changes, pharmacological therapy with β-blockers, antiarrhythmic and heart failure drugs, transcatheter ablation, ICD implantation, and cardiac transplantation.

Lifestyle Changes

Given the well-known association between endurance sports and five-time increased risk of SCD, patients with a definitive diagnosis of ARVC and asymptomatic mutation carriers should not participate in any competitive activity [14]. No absolute contraindications in practicing low-intensity physical activity are established, especially for ARVC patients treated with β-blockers.

β-Blockers and Antiarrhythmic Therapy

With the assumption that the adrenergic stimulation during exercise triggers arrhythmias, treatment with β-blockers currently represents a first-choice therapy in patients with a definitive diagnosis of ARVC. In contrast, β-blockers are not usually recommended in mutation carriers who do not express the ARVC phenotype.

Antiarrhythmic medications, in association with β-blockers or alone, may be useful to reduce ventricular arrhythmias frequency and symptoms in patients with ARVC. Although there is no evidence to suggest a specific antiarrhythmic treatment, class III drugs as amiodarone and sotalol are the drugs of choice [1]. However, any antiarrhythmic medication has demonstrated to reduce the risk of SCD; as a result, antiarrhythmic drug therapy should not be considered an equivalent alternative to ICD implantation in ARVC patients.

ICD Implantation and Arrhythmic Risk Stratification

In patients with ARVC and documented sustained ventricular fibrillation or VT (PV), ICD implantation for secondary prevention is strongly recommended. In these patients, appropriate ICD intervention occurs in about 10 % of cases per year, and the estimated survival benefit is about 25–30 % at 3 years follow-up [2].

On the contrary, due to the relatively low prevalence of the disease and lack of randomized controlled trials, the indications for ICD implantation for primary prevention are still object of intense debate among experts.

Prognostic stratification and indications for ICD implantation for primary prevention are currently based on several arrhythmic risk factors, mostly identified from retrospective studies or autopsy data, such as unexplained syncope; proband status; young age; physical activity; family history for SCD, QRS, and QT dispersion; severe right ventricular dysfunction; left ventricular involvement; and inducible VT [15]. However, not all these risk factors should be taken into account when an ARVC patient is evaluated for ICD implant.

An interesting pyramidal representation of the relationship between the arrhythmic risk and current ICD implant indications for ARVC patients was proposed by Corrado and colleagues [4]. At the apex of the pyramid, there are the high-risk patients who are most likely to benefit from an

Table 14.2 Our approach to patients with ARVC according to the arrhythmic risk

Subgroups	Risk markers	Recommendations	ICD indication
High risk (8–10 %/year)	Aborted SCD Hemodynamically unstable sustained VT	Avoid competitive sport β-blockers	Recommended
Moderate risk (1–2 %/year)	Unexplained syncope Hemodynamically stable sustained VT Non-sustained VT	Avoid competitive sport β-blockers Annually FU including: ECG Cardiac imaging (ECHO vs. CMR) Holter Exercise stress testing	Consider
Moderate risk (?%/year)	Severe dilatation and/or dysfunction of RV, LV, or both Early onset structurally severe disease (age < 35 years)	Avoid competitive sport β-blockers Annually FU including: ECG Cardiac imaging (ECHO vs. CMR) Holter Exercise stress testing	Consider
Low risk (<1 %/year)	Asymptomatic mutation carriers ARVD patients without risk factors	Reduce physical exercise Avoid competitive sport Annually FU including: ECG Cardiac imaging (ECHO vs. CMR) Holter Exercise stress testing	Not recommended

ARVD arrhythmogenic right ventricular dysplasia, *FU* follow-up, *CMR* cardiac magnetic resonance, *LV* left ventricle, *RV* right ventricle, *SCD* sudden cardiac death, *VT* ventricular tachycardia, *ICD* internal cardiac defibrillator

ICD such as those with previous heart attack, unstable hemodynamic VT, and unexplained syncope. By contrast, at the bottom, there are patients with definitive diagnosis of ARVC but without arrhythmic risk factors and patients who are mutation carriers who do not express the ARVC phenotype. For these low-risk patients, ICD implantation is not generally recommended. Patients with intermediate risk, linked to the detection of non-sustained VT or demonstration of a moderate-severe ventricular dysfunction, are represented in the middle of the pyramid. In these patients, the indication to implantation of the ICD must be evaluated taking into account both the arrhythmic profile and the risk of potential implant complications, costs, and the psychological impact, especially for the young. According to these stratification risks, our approach in patients with ARVC is described in Table 14.2.

Radiofrequency Ablation

The radiofrequency ablation is not a definitive therapy for ventricular arrhythmias and should not be considered an equivalent alternative to ICD implantation in high-risk patients for SCD. This therapeutic approach may be appropriate in selected ARVC patients who are not candidates for ICD implantation or who are ICD recipients with frequent VT episodes and ICD shocks despite antiarrhythmic therapy [1]. The ablative technique may include a multiple epicardial and endocardial mapping approach due to the multifocal nature of the disease.

Cardiac Transplantation

In rare cases, patients with ARVC who develop heart failure symptoms or refractory ventricular arrhythmias may be candidates for heart transplantation.

Conclusions

ARVC is a genetic disease of the myocardium with hereditary transmission in half of cases and associated with an increased risk of SCD. The diagnosis is complex and, if missed, can be fatal. The therapy goal is the SCD prevention. Although the benefit of the implantation of the ICD in a patient who survived to a cardiac arrest is universally recognized, the role of the ICD for primary prevention is still being debated.

References

1. Zipes DP et al (2006) ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 48(5):e247–e346
2. Basso C et al (2009) Arrhythmogenic right ventricular cardiomyopathy. Lancet 373(9671):1289–1300
3. Thiene G et al (1997) Arrhythmogenic right ventricular cardiomyopathy a still underrecognized clinic entity. Trends Cardiovasc Med 7(3):84–90
4. Corrado D et al (2011) Molecular biology and clinical management of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart 97(7):530–539
5. Marcus FI et al (1982) Right ventricular dysplasia: a report of 24 adult cases. Circulation 65(2):384–398
6. Camm CF et al (2013) Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Heart Rhythm 10(11):1661–1668
7. Sen-Chowdhry S et al (2007) Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. Circulation 115(13):1710–1720
8. McKenna WJ et al (1994) 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 71(3):215–218
9. Marcus FI et al (2010) Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 121(13):1533–1541
10. Marcus FI, Zareba W (2009) The electrocardiogram in right ventricular cardiomyopathy/dysplasia. How can the electrocardiogram assist in understanding the pathologic and functional changes of the heart in this disease? J Electrocardiol 42(2):136.e1–5
11. O'Donnell D et al (2003) Clinical and electrophysiological differences between patients with arrhythmogenic right ventricular dysplasia and right ventricular outflow tract tachycardia. Eur Heart J 24(9):801–810
12. Ackerman MJ et al (2011) HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm 8(8):1308–1339
13. Cooper LT et al (2007) The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. Eur Heart J 28(24):3076–3093
14. Pelliccia A et al (2006) Recommendations for participation in competitive sport and leisure-time physical activity in individuals with cardiomyopathies, myocarditis and pericarditis. Eur J Cardiovasc Prev Rehabil 13(6):876–885
15. Basso C et al (2012) Arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol 5(6):1233–1246