# Arrhythmogenic Right Ventricular Cardiomyopathy: Clinical Assessment and Differential Diagnosis

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## 14.1 Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiovascular disorder characterized by myocyte loss and fibrofatty tissue replacement leading to life-threatening ventricular arrhythmias, progressive ventricular dysfunction of the right (RV) and left ventricle (LV), and heart failure (HF) [1, 2]. The estimated prevalence of ARVC in the general population ranges from 1:2,000 to 1:5,000 individuals; men are more frequently affected than women, with an approximate ratio of 3:1 [3]. A familial history of ARVC is present in 30–50 % of cases, and the disease is usually inherited in an autosomal dominant pattern, with variable penetrance and expressivity, although autosomal recessive forms are also reported (Naxos disease and Carvajal syndrome). ARVC is considered to be a disease of myocyte adhesion caused by defects at the intercellular junctions. Cardiac myocyte-to-myocyte adhesion is maintained by desmosomes, adherens junctions, and gap junctions, which together comprise the intercalated disc.

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A genetic defect can be confirmed in approximately 40 % of cases, and 12 different ARVC loci have been reported, among which five genes (*DSP, PKP2, DSG2, DSC2,* and *JUP*) encode proteins of cell–cell junctions at the intercalated disc. The role of the other three nondesmosomal genes is well established: transforming growth factor beta-3 (*TGF-β3*), the ion-channel subunit *RYR2*, and the transmembrane protein 43 (*TMEM43*) [4]. Novel variants in the giant sarcomeric protein titin (*TTN*) are also associated with ARVC [5]. Structural impairment of titin, which probably leads to proteolysis and apoptosis, constitutes to be a novel mechanism underlying myocardial remodeling and sudden death (SD).

## 14.2 Clinical Features

ARVC onset usually occurs after childhood, with palpitations and/or syncope. In some cases, severe ventricular arrhythmias are the first presentation of the disease and lead to SD. Since 1995, a recessive form of ARVC has been recognized with a distinct phenotypic expression and cardiocutaneous aspects characterized by palmoplantar keratoderma and woolly hair, well known as Naxos disease. Furthermore, ARVC is the second most frequent cause of SD in young adults and athletes, and cardiac arrest may occur in up to 50 % of index cases [6]. According to Dalal et al. [7], the median age at onset is 29 years. It is rare to manifest clinical signs or symptoms of ARVC before the age of 12 years or after the age of 60 years.

According to the Padua group [8], the natural history of ARVC may be separated into four distinct phases, with progressive development of symptoms and structural abnormalities:

1. Concealed phase: This phase is characterized by minor arrhythmias that usually go unnoticed and subtle or absent structural RV abnormalities. The diagnosis is usually made during family screening in asymptomatic individuals. SD may be the first and unique manifestation of the disease at this initial stage.
2. Overt electrical disorder with palpitations, syncope, and ventricular arrhythmias of RV origin: This manifestation is usually triggered by effort. Arrhythmias range from isolated premature ventricular beats to nonsustained ventricular tachycardia with left bundle-branch block (LBBB) morphology up to ventricular fibrillation leading to cardiac arrest.
3. RV failure due to progressive myocardial fibrofatty replacement: This manifestation leads to RV enlargement and systolic dysfunction with consequent HF.
4. Biventricular failure, which usually develops late in the natural history of the disease: Progressive structural abnormalities involve the LV, with symptoms of overt congestive HF. In such conditions, contractile dysfunction may be so severe as to require cardiac transplantation. Endocavitary mural thrombosis may occur, especially within RV aneurysms or in the atria in the presence of atrial fibrillation (AF). The ultimate phenotype may resemble features of dilated cardiomyopathy (DCM) with biventricular involvement, making differential diagnosis difficult.

The diagnosis of ARVC is often challenging due to heterogeneous clinical presentation, highly variable intra- and interfamily expressivity, and incomplete penetrance. This genotype–phenotype plasticity is as yet largely unexplained.

## 14.3 Diagnosis

There is no single gold-standard diagnostic test for ARVC. Therefore, diagnosis relies on a scoring system, with major and minor criteria based on demonstration of a combination of abnormalities in RV morphology and function, typical depolarization/repolarization electrocardiographic (ECG) changes (Fig. 14.1), peculiar histological findings, ventricular arrhythmias, family history, and results of genetic testing. Definitive diagnosis, based on the Revised 2010 Task Force Criteria [9] (Table 14.1), requires two major criteria, one major plus two minor criteria, or four minor criteria from different categories. Therefore, initial evaluation of all patients suspected of having ARVC should include physical examination; clinical history; family history of ARVC or arrhythmias or SD; ECG; signal-averaged ECG; 24-h Holter monitoring; and comprehensive nonechocardiography focused on both ventricles. This imaging technique can reveal RV structural abnormalities such as RV dilation, aneurysm formation, and functional abnormalities, including hypo-a-dyskinetic RV regions, RV systolic dysfunction, paradoxical septal motion, and tricuspid regurgitation [10]. In the late stages, LV involvement with biventricular failure is observed. New tools for improving diagnostic accuracy are now available in clinical practice. Among noninvasive investigations, cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) can detect myocardial fibrosis

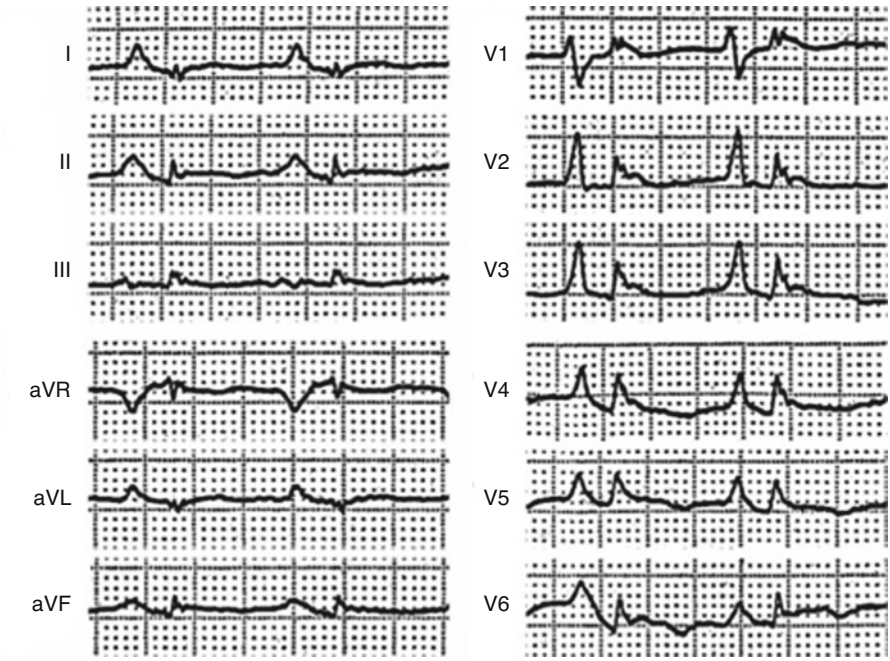


**Fig. 14.1** Typical electrocardiogram (ECG) in advanced arrhythmogenic right ventricular cardiomyopathy (ARVC). Right atrial enlargement, low QRS voltages, epsilon waves, and negative T waves in anterior precordial leads are present

**Table 14.1** Revised Task Force Criteria 2010

| | Major criteria | Minor criteria |
|---|---|---|
| RV systolic function and structure | By 2D echo:<br>Regional RV akinesia, dyskinesia, or aneurysm and one of the following (end diastole):<br>PLAX RVOT ≥32 mm,<br>PSAX RVOT ≥36 mm, or fractional area change ≤33 %<br>By MRI:<br>Regional RV akinesia, dyskinesia or aneurysm or dyssynchronous RV contraction and one of following:<br>Ratio of RV end-diastolic volume to BSA ≥110 ml/m$^2$ or ≥100 ml/m$^2$ (or RVEF ≤40 %)<br>By RV angiography:<br>Regional RV akinesia, dyskinesia, or aneurysm | By 2D echo:<br>Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole):<br>PLAX RVOT ≥29 to <32 mm,<br>PSAX RVOT ≥32 to <36 mm, or fractional area change >33 to ≤40 %<br>By MRI:<br>Regional RV akinesia, dyskinesia or aneurysm or dyssynchronous RV contraction and 1 of the following:<br>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 >40 to ≤45 %<br>By RV angiography:<br>Regional RV akinesia, dyskinesia, or aneurysm |
| Tissue characterization | Residual myocytes <60 % by morphometric analysis, with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB | Residual myocytes 60–75 % (or 50–65 % if estimated), with fibrous replacement of RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB |
| Repolarization abnormality | Inverted T waves in right precordial leads (V1–3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120 ms | Inverted T waves in leads V1 and 2 in individuals >14 years (in absence of complete RBBB) or in V4–6 or inverted T waves in leads V1–4 in individuals >14 years (in presence of complete RBBB) |
| Depolarization abnormality | Epsilon waves in the right precordial leads (V1–3) | Late potential by SAECG in ≥1 of 3 parameters in absence of QRS duration ≥110 ms on standard ECG; filtered QRS duration ≥114 ms; terminal QRS duration <40 μV or ≥38 ms; root-mean-square voltage of terminal 40 ms ≤20 μV; QRS terminal activation duration ≥55 ms measured from S-wave nadir to end of QRS |
| Arrhythmias | Nonsustained or sustained ventricular tachycardia of LBB morphology with superior axis<br>Frequent ventricular extrasystoles (>1,000 per 24 h) (Holter) | Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBB morphology with inferior axis, or >500 ventricular extrasystoles per 24 h (Holter) |
| Familial history | ARVC confirmed pathologically in the first degree or identification of a pathogenic mutation categorized as associated or probably associated with ARVC | History of ARVC in a first-degree relative or premature sudden death (<35 years) due to suspected ARVC or ARVC confirmed pathologically, or by Task Force Criteria in second-degree relative |

*RV* right ventricle, *PLAX* parasternal long axis, *RVOT* right ventricular outflow tract, *PSAX* parasternal short axis, *MRI* magnetic resonance imaging, *BSA* body surface area, *EMB* endomyocardial biopsy, *RBBB* right bundle-branch block, *LBB* left bundle branch, *SAECG* signal averaged electrocardiograph, *ARVC* arrhythmogenic right ventricular cardiomyopathy (Modified from Marcus et al. [9])

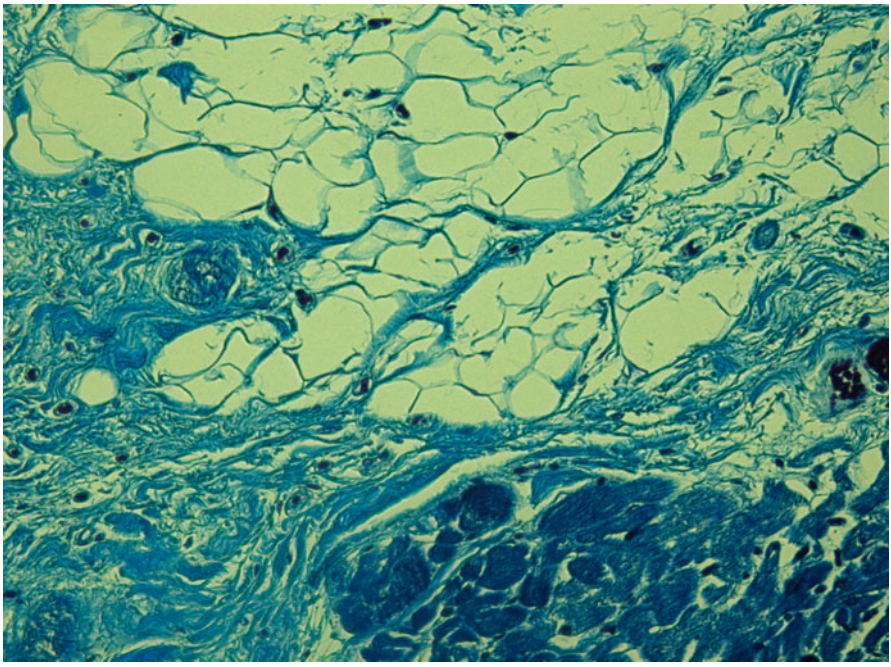

**Fig. 14.2** Histologic specimen (Azan Mallory, ×20) at the right ventricular level in a case of arrhythmogenic right ventricular cardiomyopathy (ARVC). Severe fatty infiltration associated with patchy and interstitial fibrosis (*blue*) is present

and intramyocardial fatty infiltration. CMR allows the clearest visualization of the RV (for dilatation, dysfunction, regional wall motion abnormalities, and aneurysm formation) [11].

Diagnosis of ARVC remains a clinical challenge, particularly in its early stages and in patients with minimal echocardiographic RV abnormalities and especially in the absence of structural changes in the typical triangle of dysplasia [subtricuspid region, RV outflow tract (OT), and RV inferoapical region] [12]. Positive endomyocardial biopsy (EMB) of the RV is a recognized gold standard, but it often yields a false-negative result (sensitivity ~67 %) because of the frequently localized fibroadipose infiltration. Consequently, the best approach in making a diagnosis of ARVC is by combining different diagnostic tests [9, 13]. The histological hallmark of the disease is fibrofatty infiltration of the RV myocardium with areas of surviving myocytes (Fig. 14.2) and sometimes inflammatory infiltration. Pathologic abnormalities can progress with time, typically starting from the epicardium and eventually extending down to reach the subendocardium and becoming transmural. This implies a weakness and thinning of the free wall, resulting in RV dilatation and aneurysm formation, bulges, and sacculations, which constitute the typical diagnostic findings on noninvasive imaging tests [14].

LV involvement, typically affecting the posterior and lateral walls, is present in more than half of ARVC cases [15, 16]. The frequent, and sometimes predominant, LV involvement suggests that ARVC is not a unique entity but a complex disease,

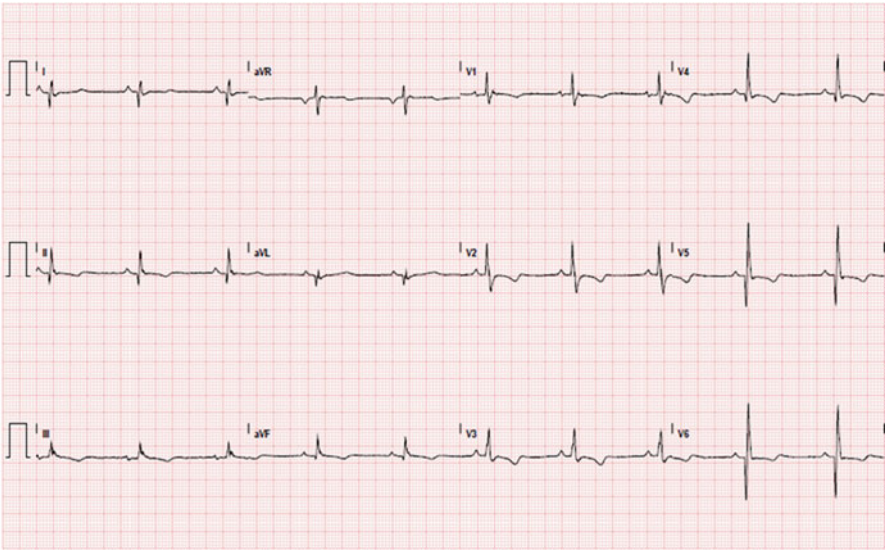


**Fig. 14.3** Electrocardiogram (ECG) of a patient with arrhythmogenic right ventricular cardiomyopathy with biventricular involvement. Sinus rhythm; epsilon waves in V1; inverted T waves in right precordial leads; negative T waves from V4 to V6 and inferior leads; deep Q waves in inferolateral leads

with three possible patterns of expression: classic right-dominant (39 % of cases), left-dominant arrhythmogenic cardiomyopathy (LDAC) (5 %), and biventricular (56 %) forms [17, 18]. Interestingly, recent data showed that the LV may be affected not only in the late stage of the disease but may also occur in absence of alterations in RV systolic dysfunction, characterizing the LDAC form of the disease [16]. This left-dominant pattern is characterized by predominant LV involvement (dilation, systolic impairment, LGE) exceeding that of the RV or in the presence of preserved RV function [19]. Other features of this pattern are the LV origin of arrhythmias (RBBB morphology), inferolateral T-wave inversion on ECG (Fig. 14.3), and family history of LDAC.

### 14.3.1 Differential Diagnosis

Diagnosis of ARVC should be considered in any patient who does not have known heart disease and who presents with frequent premature ventricular contractions or symptomatic ventricular tachycardia. The main differential diagnoses include the following conditions:

1. Idiopathic RV outflow tract/ventricular tachycardia is a mostly benign condition that is not associated with structural heart disease. In its early stage, ARVC can be difficult to distinguish from this idiopathic type of ventricular arrhythmia in

**Table 14.2** Clinical expressions of RVOT VT and ARVC

| | RVOT VT | ARVC |
|---|---|---|
| Age at onset | Third or fifth decade of life | Third or fourth decade of life |
| Sex | Females predominantly | Males predominantly |
| Family history | – | + |
| Reports of SD | – | + |
| 12-lead ECG | Normal | T-wave inversion in precordial leads V1–5<br>Prolongation of QRS complex in leads V1 or V2<br>Epsilon waves observed |
| SAECG | Normal | Late potentials observed |
| ECHO | Normal | Structural and wall motion abnormalities of RV |
| Arrhythmias | PVCs, repetitive monomorphic VT, induced/sustained VT | PVCs, SVT, NSVT, VF |
| Origin of arrhythmia | Septum | Parietal wall |
| Mechanism of arrhythmia | cAMP-mediated triggered activity | Reentrant mechanism |
| BNP levels | Normal | Increased |

Modified from Steckman et al. [22]
*RVOT* right ventricular outflow tract, *VT* ventricular tachycardia, *SD* sudden death, *ECG* electrocardiogram, *SAECG* signal-averaged ECG, *ECHO* echocardiography, *BNP* brain natriuretic peptide, *PVC* polymorphic ventricular tachycardia, cAMP cyclic adenosine monophosphate, *SVT* sustained ventricular tachycardia, *NVST* nonsustained ventricular tachycardia, *VF* ventricular fibrillation

the absence of structural changes. Differential diagnosis is based on the fact that this arrhythmia is nonfamilial, and patients do not have the characteristic ECG/signal average ECG abnormalities of ARVC (inversion T waves in V1–V3, epsilon waves, QRS duration >110 ms) (Table 14.2) [20].

2. Brugada syndrome is an inherited cardiac condition that, similarly to ARVC, is transmitted with an autosomal dominant pattern, which can lead to SD from malignant ventricular arrhythmias. Conversely, it is also characterized by a distinct typical ECG pattern, with J wave in precordial leads (Fig. 14.4) and by the absence of morphological echocardiographic features.
3. Dilated cardiomyopathy may be difficult to distinguish from ARVC, especially in its advanced stage with severe biventricular involvement. In this late phase, signs and symptoms of RV and/or LV failure can be present; finally, severe biventricular congestive HF can occur. In the absence of classic ARVC hallmarks (RV aneurysms, bulging), clinical distinction between these two CMP can be extremely difficult or impossible. Table 14.3 shows some differences between these two pathologies that are useful in differential diagnosis.
4. Myocarditis can mimic ARVC, especially when the RV is involved. Myocarditis can cause structural abnormalities, including microaneurysms, as well as the arrhythmic manifestations considered typical of ARVC. Moreover, myocardial inflammatory infiltrates, myocyte necrosis, and replacement fibrosis may lead to

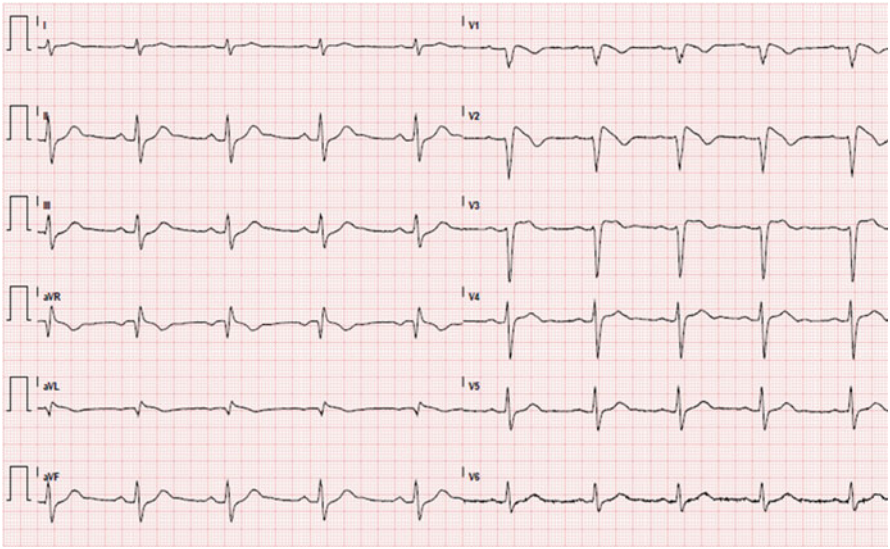


**Fig. 14.4** Electrocardiogram (ECG) of a patient with Brugada syndrome: sinus rhythm. In precordial leads (V1–3), a typical type 1 pattern is present. "Coved-type" ST elevation with at least 2 mm (0.2 mV) J-point elevation, gradually descending ST segment, followed by a negative T wave

**Table 14.3** Differential diagnosis between ARVC with biventricular involvement and DCM

| | ARVC (biventricular) | DCM |
|---|---|---|
| Main dilatation | RV | LV |
| Main dysfunction | RV (or biventricular) | LV (or biventricular) |
| Aneurysm | RV (+/–LV) | Rare |
| Fibro-fatty tissue | RV (+/–LV) | – |
| Pulmonary hypertension | – | +/– |
| Family history | + | +/– |
| Epsilon waves (ECG) | +/– | – |
| Ventricular morphology of arrhythmias | LBBB or polymorphic morphology | RBBB or polymorphic morphology |

*ARVC* arrhythmogenic right ventricular cardiomyopathy, *DCM* dilated cardiomyopathy, *LV* left ventricle, *RV* right ventricle, *LBBB* left bundle branch block, *RBBB* right bundle branch block

functional and structural changes in the RV myocardium, resembling those produced by ARVC fibrofatty replacement. New tools, such as 3D electroanatomic mapping, applied to the standard EMB, have been introduced to improve diagnostic accuracy in clinical practice. In a provocative study, Pieroni et al. [21] found that 50 % of patients with a diagnosis of noninvasive ARVC fulfilled Dallas histological criteria of active myocarditis. These data require confirmation in large patient populations.

5. Sarcoidosis with cardiac involvement can mimic ARVC, making accurate differential diagnosis more challenging. It must be considered if conduction defects with a high-grade atrioventricular block, respiratory, or systemic symptoms are present. Global RV hypokinesis or some regional wall motion abnormalities can be present due to the patchy nature of the granulomatous infiltration. Both sarcoidosis and ARVC can be progressive pathologies, and the accuracy of CMR could vary depending on the stage of the disease at which CMR data are acquired. The absence of myocardial fat infiltrates at CMR could be a useful distinguishing feature by which to suspect sarcoidosis [22].
6. Other pathologies:
   (a) Coronary artery disease and myocardial infarction can involve both ventricles and mimic aspects of ARVC.
   (b) Pulmonary hypertension (RV-pressure overload) and tricuspid regurgitation (RV-volume overload secondary to increasing stroke volume) can cause RV dilation and dysfunction.
   (c) Congenital heart diseases, such as Uhl anomaly (a rare congenital heart disease with a partial or total loss of the RV myocardial muscle) [22] and repaired tetralogy of Fallot must be considered, especially for their prevalent RV involvement.
   (d) Intracardiac shunts (e.g., atrial septal defects and anomalous pulmonary venous drainage) may cause RV volume overload. The diagnosis can be missed on standard echocardiogram, and in this cases, transesophageal echocardiography (TEE) and/or CMR (which have excellent correlation with RV angiography) can improve diagnostic accuracy.

**Conclusions**

ARVC is a frequently progressive disease with risk of life-threatening complications and which constitutes a clinical diagnostic challenge for physicians given the different genotypic and phenotypic variations and the wide ranges of clinical manifestations. Genetic studies indicate that ARVC should be considered a disease of desmosome dysfunction. Its diagnosis is based on the modified Task Force Criteria for ARVC [9] and should be approached with great caution. The main challenge is to improve risk stratification in relation to SD and HF and identify patients who will most benefit from early intervention involving lifestyle changes, restriction of physical sport activity, antiarrhythmic drugs, and/or ICD placement.

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