REVIEW

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/D): A Systematic Literature Review

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Abstract: Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic form of cardiomyopathy (CM) usually transmitted with an autosomal dominant pattern. It primary affects the right ventricle (RV), but may involve the left ventricle (LV) and culminate in biventricular heart failure (HF), life threatening ventricular arrhythmias and sudden cardiac death (SCD). It accounts for 11%–22% of cases of SCD in the young athlete population. Pathologically is characterized by myocardial atrophy, fibrofatty replacement and chamber dilation.

Diagnosis is often difficult due to the nonspecific nature of the disease and the broad spectrum of phenotypic variations. Therefore consensus diagnostic criteria have been developed and combined electrocardiography, echocardiography, cardiac magnetic resonance imaging (CMRI) and myocardial biopsy. Early detection, family screening and risk stratification are the cornerstones in the diagnostic evaluation. Implantable cardioverter-defibrillator (ICD) implantation, ablative procedures and heart transplantation are currently the main therapeutic options.

Keywords: Arrhythmogenic right ventricular cardiomyopathy (ARVC/D), cardiomyopathy, sudden cardiac death, tachyarrhythmias

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic form of cardiomyopathy that primarily affects the right ventricle (RV). It may also involve the left ventricle (LV) and culminate in life-threatening ventricular arrhythmias, prompting sudden cardiac death (SCD) and/or biventricular heart failure.[1–5] ARVC/D was first described by the Pope's physician, Giovanni Maria Lancisi, in his book entitled *De Motu Cordis et Aneurysmatibus,* published in 1736.[6] He reported that there was a family who had experienced pathologic RV, heart failure and SCD in four generations. The first comprehensive clinical description of the disease was reported by Marcus et al in 1982, when he reported 24 adult cases with ventricular tachyarrhythmias with left bundle branch morphology.[7] Nevertheless, it was not until 1984 that the electrocardiographic features of the disease were first described, including the epsilon wave.[8]

ARVC/D is characterized pathologically by myocardial atrophy, fibrofatty replacement, fibrosis and ultimate thinning of the wall with chamber dilation and aneurysm formation.[9] These changes consequently produce electrical instability precipitating ventricular tachycardia (VT) and SCD.[10–20]

Epidemiology

The estimated prevalence of ARVC/D in the general population is approximately 1:5000, affecting men more frequently than women with a ratio of 3:1.[21,22] ARVC/D accounts for 11%–22% of cases of SCD in the young athlete patient population,[23–25] accounting for approximately 22% of cases in athletes in northern Italy[26] and about 17% of SCD in young people in the United States.[27]

It has been difficult to determine the incidence of ARVC/D due to the different clinical manifestations of the disease. These manifestations vary greatly, especially in different ethnic groups. This is probably secondary to its genetic heterogeneity and variable phenotypic expression, along with a diverse disease progression, which make diagnosis difficult, and in turn, decreases the real incidence evaluation of this entity.

These ethnic variations are likely caused by different modes of inheritance and involved genes. For instance, in Naxos Island, Greece, the mode of inheritance of ARVC/D in association with palmoplantar keratosis, also known as Naxos disease, was demonstrated to be autosomal recessive,[28] whereas the mode of inheritance in most of ARVC/D is autosomal dominant. Other studies suggest that Chinese patients may have a lower familial incidence of premature SCD among ARVC/D patients compared to Western population, although there is no genetic data on this population.[29]

Disease Genetics and Pathogenesis

ARVC/D was initially believed to be secondary to a developmental defect of the RV myocardium, leading to the original designation of "dysplasia", similar to Uhl's anomaly.[30] Nonetheless, this process differs from ARVC/D based on the fact that Uhl's anomaly has not been documented to have a genetic basis, and it is not recognized as a desmosomal disease. In addition, myocardial atrophy is the consequence of cell death after birth and its progressive postnatal development has been definitively assessed (See Table 1).[26,31,32] This concept has evolved over the last 30 years and based on its clinical characteristics, pathophysiology, post-natal development and genetic background, its inclusion in the World Health Organization (WHO) classification of cardiomyopathies was finally achieved.[33,34]

Several studies have been performed to determine the etiology and pathogenesis of ARVC/D. However, there still is conflicting evidence. Different causes have been suggested such as congenital defects, genetics and acquired factors. The hypothesis of a congenital cause leads to the adoption of the term dysplasia due to its association with Uhl's anomaly, as explained earlier, but ARVC/D has been differentiated and its natural history through adult life has been well documented.[3,30] This hypothesis has evolved into the idea of genetically determined cardiomyopathy, which has been retained on genetic grounds.[33,34] In approximately 30%–50% of cases it is transmitted with an autosomal dominant pattern of inheritance, with incomplete penetrance and variable expression.[35–37]

Acquired factors have also been suggested as the cause of ARVC/D. The strongest association has been made with viral myocarditis inducing arrhythmogenic cardiomyopathy. On histopathology, a lymphocytic infiltrate with disappearance of myocytes and fibrofatty replacement is often found, which can also

Table 1. Differences between Uhl's anomaly and ARVC/D.

	Mode of Inheritance	Pathogenic Mechanisms	Age at presentation	Presentation	Disease's progression
Uhl's Anomaly	Rarely familial	Apoptotic dysplasia with complete absence of the myocardium[32]	Usually is diagnosed in neonatal or infant life. Male:female ratio 1.27:1[31,32]	Cyanosis, dyspnea, RV dilation and heart failure	Does not progress
ARVC/D	Most autosomal dominant, some variants are inherited in a recessive pattern	Apoptotic dysplasia of the myocardium followed by fibrofatty infiltration[32]	Usually patients present symptoms during adolescence Male:female ration 2.28:1[32]	Range from asymptomatic, palpitations, atypical chest pain to ventricular arrhythmias and heart failure	Progressive postnatal development

be seen in viral myocarditis.[38,39] It is possible that the wide variation in presentation of ARVC/D patients could be explained by its genetic heterogeneity and modifying factors such as exercise and/or viral myocarditis.[23,40,41]

The genetic hypothesis has been thoroughly studied. The first chromosomal locus identified was published by Rampazzo[44] et al in 1994 in Italy. Linkage analysis supported the evidence for genetic heterogeneity of several ARVC/D loci on chromosomes 1, 2, 3, 6, 10, 12 and 14.[42–45] Similarly, he reported the Desmoplakin gene (DSP), the first desmosomal protein gene to be associated with a major form of the disease, with autosomal dominant inheritance, also called ARVC/D type 8[46] (See Table 2).[46–51]

In addition, the gene for Naxos disease was mapped on chromosome 17 (locus 17q21), by McKoy et al.[28,43] This is the first disease-causing gene, also named *junction plakogoblin (JUP)* gene (autosomal

recessive variant of ARVC/D) characterized by palmoplantar keratosis, woolly hair and ARVC/D. The association between skin and heart manifestations could be explained by the finding that epidermal cells in the soles, palms and myocyte share a similar mechanical junctional apparatus (fascia adherens and desmosome) responsible for cell-to-cell adhesion, and are exposed to the high frictional stress. The *JUP* gene encodes the desmosomal protein, plakoglobin, a major cytoplasmic protein that is the only known constituent common to submembranous plaques of both desmosomes and intermediate junctions responsible for cell adhesion. This suggests that ARVC/D is a cell-to-cell junction disease, leading detachment of the myocytes and fibrosis, particularly under conditions of mechanical stress.[21,28,43,46,52]

A recessive mutation of DSP has been reported and associated with Carvajal syndrome, another cardiocutaneous disease.[53] Plakophilin-2 (PKP2) is the

Table 2. Different types of ARVD/C and its genetics.

Type	Gene	Locus	Prevalence	Mode of inheritance
ARVD1	*TGFB3*	14q23-q24	Rare	AD
ARVD2	*RYR2*	1q42-q43	Rare	AD
ARVD3	?	14q12-q22	Unknown	AD
ARVD4	?	2q32.1-q32.3	Unknown	AD
ARVD5	*TMEM43*	3p23	Unknown	AD
ARVD6	?	10p14-p12	Unknown	AD
ARVD7	?	10q22.3	Unknown	AD
ARVD8	*DSP*	6p24	6%–16%[46]	AD/AR
ARVD9	*PKP2*	12p11	11%–43%[47,48]	AD
ARVD10	*DSG2*	18q12.1-q12	7%–26%[49–51]	AD
ARVD11	*DSC2*	18q12.1	Rare	AD
ARVD12	*JUP*	17q21	Rare	AR

most frequent targeted protein with more than 25 different mutations identified in the gene encoding it.[52] Thus, ARVC/D was found to be mainly a disease of the cardiomyocyte junction.[54] (See Table 3).

Furthermore, extradesmosomal genes, unrelated to the cell adhesion complex, have been implicated as autosomal dominant forms of ARVC/D, such as (1) the cardiac ryanodine-2 receptor gene, responsible for the release of calcium from the sarcoplasmic reticulum; (2) the transforming growth factor-β3 gene (TGFβ3), implicated in the regulation of the production of extracellular matrix and expression of genes encoding desmosomal proteins and the TMEM43 genes.[55–57]

Clinical Presentation

ARVC/D is a devastating disease given the fact that the first symptom is often SCD, which makes early detection and a family screening test the cornerstone in the diagnostic evaluation. In a study of 100 patients with ARVC/D, Dalal et al reported an incidence of SCD of 23% in the United States. Other common presentations were palpitations (27%) and syncope (26%).[23] Early intervention with an Implantable Cardioverter-Defibrillator (ICD) decreases the risk of SCD, but ARVC/D is a progressive disease, which can progress to refractory/recalcitrant VT or a ventricular fibrillation (VF) storm despite ICD therapy.

Other studies have suggested that up to up to 67% of individuals with ARVC/D present with palpitations, 32% present with syncope, 27% with atypical chest pain, 6% with RV failure and 6% may remain asymptomatic. (See Fig. 1).[58] The most common arrhythmia is sustained or nonsustained monomorphic VT that originates in the RV and therefore has a left bundle branch block (LBBB) morphology. Alternatively, in some cases where the LV is involved, VT could present with a right bundle branch block (RBBB) morphology. These symptoms are usually exercise-related, mainly due to an activation of the sympathetic nervous system, which may lead to premature beats and re-entrant arrhythmogenic circuits. In a pathological myocardial substrate, this can perpetuate the incidence of life-threatening arrhythmias.

The advanced stage of ARVC/D is characterized by signs and symptoms of RV or LV failure depending on which ventricle is more affected (in the classic form, it is generally the RV more affected than the LV), and finally frank biventricular congestive heart failure, which may be difficult to distinguish clinically from dilated cardiomyopathy. (See Fig. 2).[58]

Clinicopathologic Manifestations

The genotypic abnormalities explained above translate into phenotypic presentations with variable penetration, leading to the anatomoclinic profile of ARVC/D.

The histological examination of the myocardium reveals a typical fibrofatty infiltration with areas of surviving myocytes and inflammation progressing from epicardium to endocardium. This infiltration may be diffuse or regional; the latter is typically located at the angles of the "triangle of dysplasia" at

Table 3. Cardiocutaneous disorders associated with ARVC/D.

|	Presentation	Genetics	Cardiac manifestations	Differences
Naxos disease	Diffuse non-epidermolytic palmoplantar keratoderma with woolly hair and cardiomyopathy	Recessive mutation of desmoplakin and plakoglobin, in C 17 (JUP gene) and C 12, but there is new evidence for extensive locus heterogeneity.	ECG is abnormal in 90% of patients, RV structural and functional abnormalities are common. Presentation is usually syncope and/or sustained ventricular tachycardia during adolescence with a peak in young adulthood.	Predominant RV involvement Fatty infiltration is common.
Carvajal syndrome	Striate palmoplantar keratoderma with woolly hair and cardiomyopathy.	A recessive mutation of desmoplakin. Gene map locus 6p24	Abnormal myocardial stretch, dilatation later fibrosis and progressive cardiac failure. Common features are: non compacted LV and recurrent VT/VF with sudden death.	Predominant LV involvement. Fatty infiltration is less common.

Symptomatology in ARVC/D
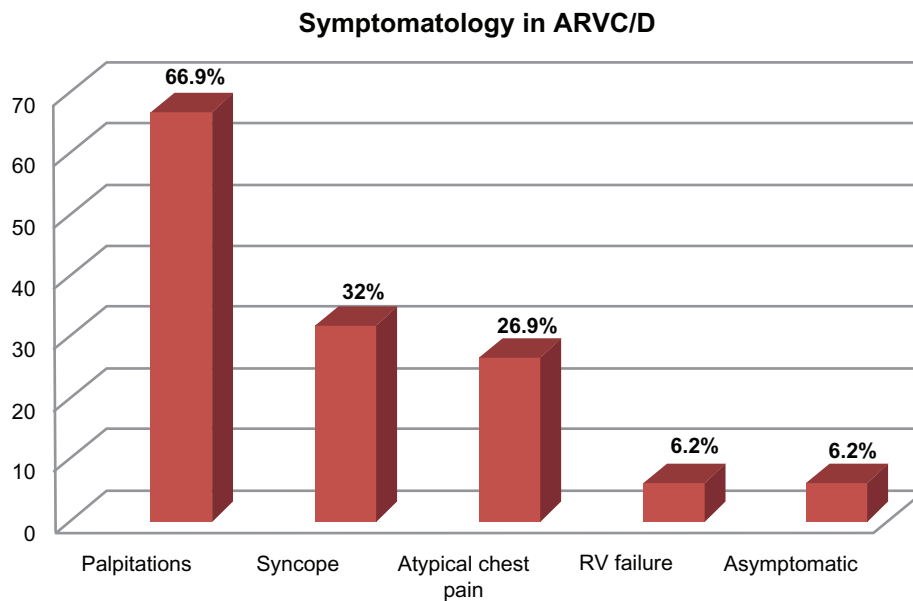
Figure 1. Presenting symptoms and frequencies in patients with ARVC/D.[58]

the infero-apical and infundibular walls. This occurs earlier in the RV, compared to the left side of the heart, but LV involvement may also sporadically occur in early stages of the disease.[8,33,59] Parietal thinning as well as endocardial thickening is found in areas of transmural infiltration and aneurismal dilation providing a substrate for life-threatening arrhythmias.

Biventricular involvement with LV fibrofatty replacement and involvement have been found as much as in 70% of the cases of ARVC/D. It is usually age dependent, associated with more severe cardiomegaly, arrhythmogenic events, inflammatory infiltrates and heart failure. ARVC/D can no longer be regarded as isolated disease of the RV.[60] Accordingly, several authors have opted for naming this condi-

Incidence

Figure 2. Incidences of ventricular involvement in ARVC/D. Classic form are mostly RV involvement, LV or Biventricular involvement.[58]

tion "Arrhythmogenic Cardiomyopathy" but the term "Right Ventricular Arrhythmogenic Cardiomyopathy" is still widely used.

The natural history of ARVC/D is highly variable, with a wide spectrum of clinical presentations. Four patterns have been proposed:[24,33] (1) Concealed form, minor arrhythmias, which usually go unnoticeable. The diagnosis is usually made during family screening.[61] (2) Overt Electrical Heart disorder, the most typical presentation, which usually occurs in young patients presenting with severe and symptomatic ventricular arrhythmias and SCD.[62] (3) RV failure, in which the myocardial replacement in the RV leads to RV dysfunction with pump failure. (4) Biventricular failure characterized by progressing dilation of RV and LV; this usually develops late in the natural history of the disease.[3,60] Other conditions have also been associated such as valvulopathies (ie, mitral valve prolapse[63] and tricuspid valve prolapse) and patent foramen ovale.[64,65] The mechanism of this association is still not known. We have postulated two different mechanisms: (1) raised left atrial pressure, as seen in patients with heart failure as they can dilate the foramen ovale leading to left-to-right shunt , while RV failure and tricuspid regurgitation can lead to rise in right atrial pressure and cause right-to-left shunt. (2) Apoptotic dysplasia, genetically determined by chromosome abnormalities, leading to loss of cell-to-cell
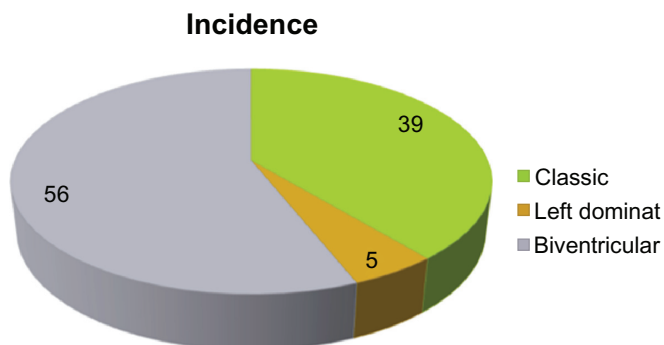
adhesion and consequently patent foramen ovale and/or valvulopathies.

It is important to emphasize that fibrofatty infiltration is possibly the least reliable criterion for the diagnosis of ARVC/D,[66] as fat may also be part of scarring from ischemia, inflammation and myocyte vacuolization, as seen in other cardiomyopathies. Therefore, its histopathological diagnosis should be done in conjunction with other features: fibrosis, tissue deposition, myocytes and inflammatory infiltration.

Diagnoses

ARVC/D should be suspected in a young patient with palpitations, syncope or aborted SCD. VT with LBBB morphology is the classic presentation, but as mentioned above, VT with RBBB may be present if the LV is involved. Other electrocardiographic abnormalities such as inverted T waves in right precordial leads (V1–V3) and frequent premature ventricular complex (PVCs), even in asymptomatic patients, should arouse the suspicion for this cardiomyopathy.[67]

Clinical diagnosis of ARVC/D is often difficult because of the non-specific nature of the disease and the broad spectrum of phenotypic variations. There is no definitive diagnostic standard. Endomyocardial biopsy (EMB) of the RV is definitive (gold standard) when positive but it often yields a false-negative result and in most patients, assessment of transmural myocardium is not possible based on the fact that the disease spreads from epicardium to endocardium. Therefore, it is not practical in the clinical setting.[68,69] The sensitivity of EMB is approximately 67% because of the regional fibroadipose infiltration.[70] Consequently, the best approach in making a diagnosis of ARVC/D is by combining different diagnostic tests.

Several investigations contribute to the diagnosis of ARVC/D. Consensus diagnostic criteria have been developed, which include RV biopsy, noninvasive electrocardiography, family history and imaging evaluation with echocardiography, cardiovascular magnetic resonance imaging (CMR) and angiography.[71,72] The advent of the molecular genetics era has made a tremendous diagnostic impact and contributed new insights to the understanding of its pathophysiology.[21]

In the last decade, enormous advances have been made, which include two research grants in Europe and USA achieved by Basso et al and Marcus et al respectively.[73,74] These have greatly contributed to the disease characterization, diagnosis, pathophysiology and therapeutic options.

The 1994 Task Force criteria were based upon clinical experience, family history, and structural, functional and electrocardiographic abnormalities in patients with severe disease.[35] Thus, these criteria have high specificity but lack sensitivity, increasing the risk of a false negative in the early stages of ARVC/D. A modification of these original criteria was made in order to include first degree relatives on early stage of the disease or incomplete expression. This increased the sensitivity, but not surprisingly also increased the risk of false positives cases.[75,76] These diagnostic criteria were revised in 2010 and now incorporate the advances in both technology and genetics (See Table 4).[72]

The diagnosis is based on the presence of major and minor criteria, which are classified into six categories. The diagnosis of ARVC/D is made in the presence of two major or one major plus two minor criteria or four minor criteria taken from different groups. (See Fig. 3).[72]

Diagnostic Modalities

- **Electrocardiogram (ECG):** almost 90% of patients with ARVC/D have some ECG abnormality. One of the most common presentations is prolonged S-wave upstroke > 55 ms in V1–V3 (90%–95%) followed by an inverted T wave on precordial leads (V1–V3), which occurs in one-half of cases presenting with VT. Inverted T waves (repolarization abnormality) are included in the 2010 Revised Task Force Criteria (see Table 4)[72] and constitute a major criterion in the absence of complete RBBB.[72,77,78] QRS prolongation (QRS > 110 msec), particularly in lead V1 has been observed in 24%–70% of patients with ARVC/D, which may be due to delayed activation of the RV rather than to any intrinsic abnormality in the right bundle branch.[79,80]

An epsilon wave (depolarization abnormality) may be found in 30%–33% of patients with ARVC/D[58] and it is described as a distinct wave at the end of QRS complex (see Fig. 4) probably secondary to slowed intraventricular conduction.

Table 4. 2010 revised task force criteria.

Major	Minor
I. Global or regional dysfunction and structural alterations*	
By 2D echo	**By 2D echo**

• Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole):
  ○ PLAX RVOT $\geq$ 32 mm (corrected for body size [PLAX/BSA] $\geq$ 19 mm/m^2)
  ○ PSAX RVOT $\geq$ 36 mm (corrected for body size [PSAX/BSA] $\geq$ 21 mm/m^2)
  ○ *or* fractional area change $\leq$ 33%
	• Regional RV akinesia or dyskinesia *and* 1 of the following (end diastole):
	  ○ PLAX RVOT $\geq$ 29 to <32 mm (corrected for body size [PLAX/BSA] $\geq$ 16 to <19 mm/m^2)
	  ○ PSAX RVOT $\geq$ 32 to <36 mm (corrected for body size [PSAX/BSA] $\geq$ 18 to <21 mm/m^2)
	  ○ *or* fractional area change > 33% to $\leq$40%

By MRI	**By MRI**

• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following:
  ○ Ratio of RV end-diastolic volume to BSA $\geq$ 110 mL/m^2 (male) or $\geq$100 mL/m^2 (female)
  ○ *or* RV ejection fraction $\leq$ 40%
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following:
	  ○ Ratio of RV end-diastolic volume to BSA $\geq$ 100 to <110 mL/m^2 (male) or $\geq$90 to <100 mL/m^2 (female)
	  ○ *or* RV ejection fraction > 40% to $\leq$45%

By RV angiography	
• Regional RV akinesia, dyskinesia, or aneurysm	
II. Tissue characterization of wall	
• Residual myocytes < 60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in $\geq$1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in $\geq$1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
• Inverted T waves in right precordial leads (V$_1$, V$_2$, and V$_3$) or beyond in individuals > 14 years of age (in the absence of complete right bundle-branch block QRS $\geq$ 120 ms)	• Inverted T waves in leads V$_1$ and V$_2$ in individuals > 14 years of age (in the absence of complete right bundle-branch block) or in V$_4$, V$_5$, or V$_6$ • Inverted T waves in leads V$_1$, V$_2$, V$_3$, and V$_4$ in individuals > 14 years of age in the presence of complete right bundle-branch block
IV. Depolarization/conduction abnormalities	
• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V$_1$ to V$_3$)	• Late potentials by SAECG in $\geq$1 of 3 parameters in the absence of a QRS duration of $\geq$110 ms on the standard ECG • Filtered QRS duration (fQRS) $\geq$114 ms • Duration of terminal QRS <40 μV (low-amplitude signal duration) $\geq$38 ms • Root-mean-square voltage of terminal 40 ms $\leq$ 20 μV • Terminal activation duration of QRS $\geq$ 55 ms measured from the nadir of the S wave to the end of the QRS, including R´, in V$_1$, V$_2$, or V$_3$, in the absence of complete right bundle-branch block
V. Arrhythmias	
• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 hours (Holter)

(*Continued*)

Table 4. (*Continued*)

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

Notes: Definite = 2 major OR 1 major + 2 minor; Borderline = 1 major + 1 minor OR 3 minor; Possible = 1 major OR 2 minor.
Modified from: Marcus FI, McKenna WJ, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation.* Apr 6, 2010;121(3):1533–41.
Abbreviations: PLAX, Parasternal Long-Axis; PSAX, Parasternal Short-Axis; RVOT, Right Ventricular Outflow Tract; BSA, body surface area.

This is also a major criterion in the 2010 revised Task Force criteria (see Table 4, IV).[72] Ventricular ectopy with LBBB morphology is also highly suggestive of ARVC/D. The origin of the ectopic beats is usually from one of the three regions of fatty degeneration in the "triangle of dysplasia". (See Table 5).[23,58,79,80]

- **Signal average electrocardiogram (SAECG):** Three criteria have been used: (1) the filtered QRS duration $\geq$ 114 ms. (2) low-amplitude signal $\geq$ 38 ms. (3) root mean square amplitude of the last 40 ms of the QRS $\leq$ 20 µV. The sensitivity improves to 69% from 47% when 1 of 3 criteria is used, instead of 2 of 3 criteria, while maintaining a high specificity of 95%. An abnormal SAECG (defined by 1 of 3 criteria) was associated with a dilated RV, an increased RV volume and a decreased RV ejection fraction on CMR.[81] (See Fig. 5[58] and Table 4, IV).[72]

- **Echocardiography:** Echocardiography reveals RV structural abnormalities such as RV dilation, aneurysm formation and functional abnormalities including hypokinetic RV, RV failure, paradoxical septal motion and tricuspid regurgitation. On late stages, LV involvement with biventricular failure is observed. In the 2010 revised Task Force criteria, echocardiographic criteria include quantitative measures of right ventricular outflow tract (RVOT) enlargement and reduction in the RV fractional area changed. These major criteria yield 95% specificity (see Table 4, I).[72]

- **Cardiovascular magnetic resonance (CMR):** CMR is widely used for the diagnosis of ARVC/D. CMR can identify global or regional ventricular dilation, dysfunction, intramyocardial fat, aneurysmatic dilation and fibrosis. Fatty infiltration of the RV is not diagnostic of ARVC/D. According to the proposed 2010 diagnostic criteria, an enlarged RV is no longer sufficient, because it may be seen in other infiltrative diseases such as sarcoidosis, amyloidosis, congenital heart diseases and pulmonary hypertension.
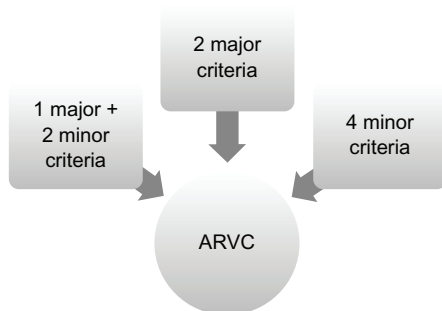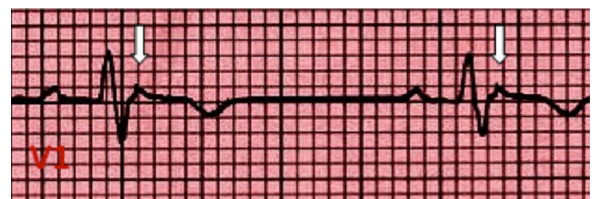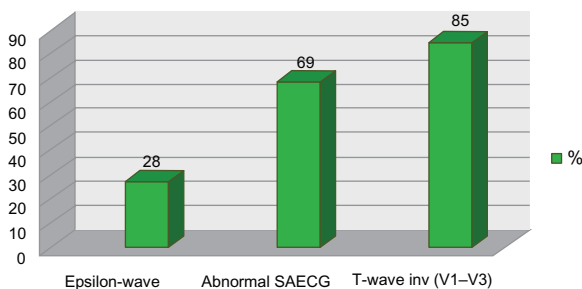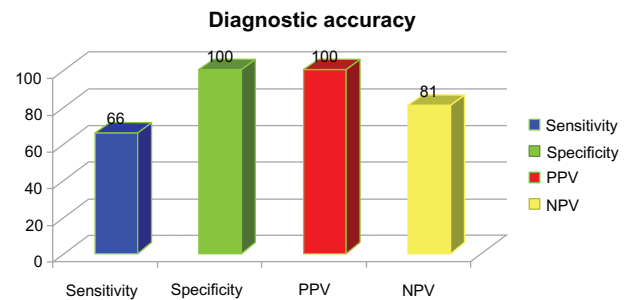

Figure 3. Diagnosis of ARVC/D: major and minor criteria.[72]

Figure 4. Epsilon wave: low amplitude positive deflection at the end of the QRS complex, usually seen in V1 and V2. If the epsilon wave is of large magnitude a reciprocal epsilon wave may be seen in V5 or V6, this may suggest that large part of the RV is depolarizing late.

Table 5. ECG changes in ARVD/C.

ECG changes	Frequency
1. Prolonged S-wave upstroke > 55 ms in V1–V3	90%–95%[23,58]
2. T waves inversion in precordial leads	82%–85%[58]
3. QRS widening in V1–3	25%–70%[58,80]
4. Epsilon wave	30%[58]
5. Right bundle branch block (RBBB)	18%–22%[58,79]
6. Paroxysmal episodes of ventricular tachycardia with a LBBB morphology	One of the most common findings

Figure 6. Diagnostic accuracy of noninvasive detection of myocardial fibrosis in arrhythmogenic right ventricular cardiomyopathy using delayed-enhancement magnetic resonance imaging.[82.]

The diagnostic criteria now require the presence of akinesia, dyskinesia or aneurysm in addition to a decreased RV ejection fraction or increased RV end diastolic volume to body surface area ratio (see Table 4, I).[72] More recently, delayed enhancement CMR (DE MRI) has been proposed and tested in the diagnosis of ARVC/D, particularly for the detection of fibrotic tissue. In a recent study by Tandri et al,[82] this technique showed a sensitivity of 66% with a specificity of 100% as well as a PPV of 100% and a NPV of 81%. These values make this modality very attractive and promising in making the diagnosis of ARVC/D. (See Fig. 6). Diagnosis accuracy of cardiac Delayed Enhanced Magnetic Resonance Imaging (DE-MRI).[82] (See Fig. 7).

- **Right ventricular angiography:** The 2010 revised Task Force Criteria include as a major criterion the presence of regional RV akinesis, dyskinesis or aneurysm by RV angiogram. Its specificity is 90%; however, this is a very subjective and observer-dependent test. (See Table 4, I).[72]
- **Right ventricular biopsy:** Right ventricular biopsy is highly specific but lacks sensitivity,

mainly because the fibrofatty infiltration is not uniform. The disease progression from epicardium to endocardium and most biopsy samples are taken from the ventricular septum, which is commonly not involved in the disease process. (See Fig. 8). Thus, confirmation of the diagnosis of ARVC/D by biopsy is not commonly performed. The major change is that the 2010 revised Task Force criteria creates a quantitative criteria instead of a qualitative one, which include the following as a major criterion: Residual myocytes < 60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy. (See Table 4, II).[72]

Other tests

- **Multidetector computed tomography (MDCT):** MDCT is used as an alternative to CMR for patients
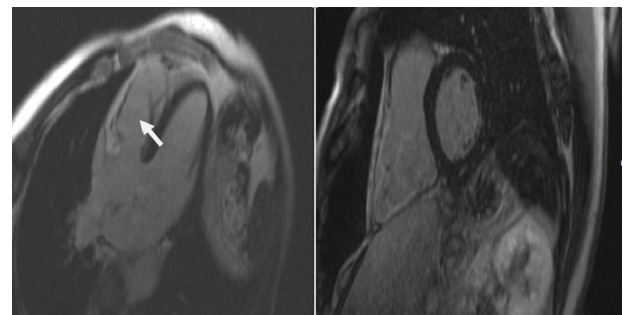
Figure 7. Delayed enhancement magnetic resonance imaging. 4-chamber and short axis views of DE-CMR showing delayed enhancement of the free right ventricular wall.
Notes: The arrow indicates the area of delayed enhancement, which represents fibrofatty replacement. The figure on the right shows a significantly dilated RV.
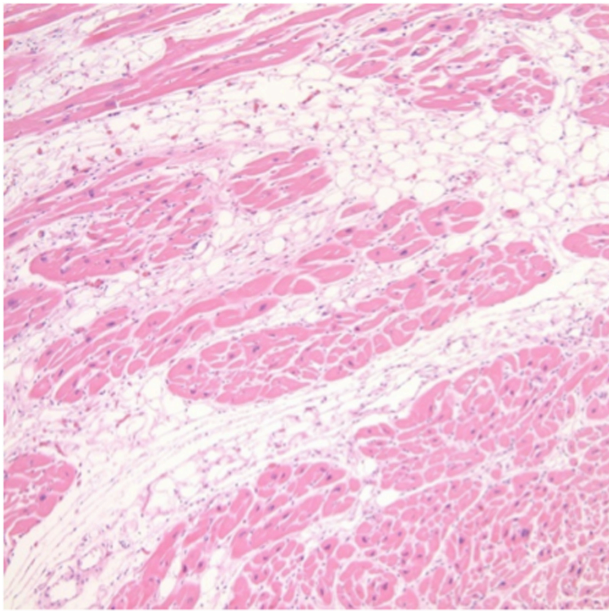

Figure 5. Incidence of ECG findings in ARVC/D.

Figure 8. The imaging is a Haematoxylin and eosin stained section and shows the typical fibrofatty infiltration of the ventricles in ARVC/D.
Note: The fibroadipose replacement advances from the epicardium to the endocardium and is associated with myocardial atrophy and myocytes loss.

Figure 9. Brugada syndrome: characterized by a dynamic ST-segment elevation (accentuated J wave) in leads V_1 to V_3 of the ECG followed by negative T wave.

in whom CMR is contraindicated. Nevertheless, CMR is a better diagnostic modality than MDCT for patients with ARVC/D.

- **Radionuclide ventriculography:** Radionuclide ventriculography can also detect regional and/or global RV dysfunction.

Despite all these different diagnostic modalities, no test is perfect. Diagnosis is difficult and requires the combination of all tests, if possible. Recent advances in technology promise to make DE MRI the imaging modality of choice to assess myocardial diseases.[82] Nevertheless, this modality is not included in the current modified Task Force criteria (See Fig. 6).[82]

Differential Diagnosis

Right ventricular outflow tract tachycardia (RVOT) is one of the main differential diagnoses of ARVC/D. The presentation and electrocardiographic characteristics of VT could be very similar in these two (VT with LBBB but with an inferior axis). However, RVOT tachycardia is considered to be a primary electrical disease in the absence of structural heart disease, unlike ARVC/D. Epidemiologically, RVOT tachycardia is more common than ARVC/D.
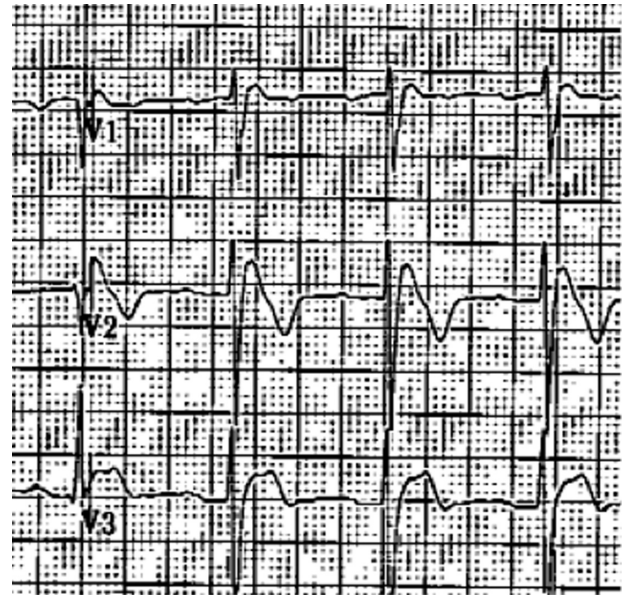
Other conditions that should be differentiated from ARVC/D are: cardiac sarcoidosis,[83] pre-excited AV re-entry tachycardia, Brugada syndrome (See Fig. 9), pulmonary hypertension, tricuspid valvulopathy and other congenital heart disease such as Uhl's anomaly (See Table 1), and repaired Tetralogy of Fallot, among others. (See Table 6).

Treatment

As discussed previously, patients with ARVC/D may remain asymptomatic or may present with a wide variety of symptoms. Therefore, the therapeutic strategy has to be individualized, based on clinical presentation, risk stratification and patient/physician preference.[22,60,83–86] The main goal of therapy is to prevent serious events, which requires identifying high-risk patients for malignant arrhythmias and SCD.[87–89]

Although several studies have evaluated the benefit of pharmacological and non-pharmacological therapies in patients with ARVC/D,[87–91] large prospective randomized trials are not available. Consequently, the current therapeutic recommendations for this entity have been developed from observational studies and case series, or have been adopted from other cardiomyopathies,[92,93] where solid evidence supported by clinical trials is available and clear guidelines are defined.[87,89]

Table 6. Differential diagnosis of ARVC/D.

Acquired heart diseases	Congenital heart disease	Miscellaneous
Tricuspid valvulopathy	Repaired tetralogy of fallot	Idiopathic RVOT tachycardia
RV infarction	Ebstein's anomaly	Pre-excited AV re-entry tachycardia
Pulmonary hypertension	Atrial septal defect (ASD)	Dystrophica myotonica
Bundle branch re-entrant tachycardia	Uhl's anomaly	Brugada syndrome
Dilated cardiomyopathy	Partial anomalous venous return	

Physical activity

Exercise has been related to an increased incidence of ventricular conduction disorders, SCD, worsening symptoms and progression of the fibrofatty atrophy,[22,78,94–96] particularly in young patients and competitive athletes.[86,97] In 1996 Leclercq et al[95] described the association between progressive sympathetic stimulation present during physical activity and the onset of monomorphic sustained VT. The initiation of the VT was associated with the typical catecholamine surge seen on exercise in the setting of the presence of arrhythmogenic substrate characteristic of these patients.[22,95] For that reason, high risk patients with suspected or confirmed ARVC/D diagnosis should avoid vigorous physical activity including competitive sports, regular training and strenuous exertion involving abrupt physical effort, as well as any recreational activity associated with symptoms (Level of Recommendation: IB).[96–98]

Pharmacological therapy

Antiarrhythmic medications have been used for symptomatic control in patients who are not candidates for an implantable cardioverter-defibrillator (ICD) or as an adjunct therapy to reduce frequent ICD discharges due to recurrent VT.[89,99] Antiarrhythmic medications have been mostly recommended in patients with severe LV dysfunction and severe symptoms of ventricular arrhythmias. Beta-adrenergic blocking agents have shown effectiveness in reducing adrenergically-stimulated arrhythmias.[22,85,100,101] Nevertheless, the evidence available has been derived from observational studies, which have shown conflicting results.

The combination of beta-blockers and amiodarone[100] have had a beneficial effect in suppression of non-sustained VT, reduction in the frequency of sustained ventricular arrhythmias,[91] and reduction of VT rate preventing syncope and favoring antitachycardia pacing termination rather than shock therapy. Furthermore, they favor the suppression of other arrhythmias, especially supraventricular tachycardia (SVT) and atrial fibrillation which may cause symptoms or interfere with ICD function, resulting in inappropriate discharges.[91]

Sotalol and amiodarone have been proposed as effective treatment of sustained VT or ventricular fibrillation (VF) as adjunctive therapy to ICD or in patients with ARVC/D that are not candidates for ICD implantation (Level of Recommendation: IIaC).[89,91,99] In 1992, Wichter et al[91] published that sotalol was the most effective medication in the treatment of both inducible and non-inducible VT with efficacy rates of 68.4 and 82.8% respectively, in patients with ARVC/D; patients who did not respond to sotalol were non-responders to other antiarrhythmic therapies including amiodarone. Class I antiarrhythmic drugs were effective in only a minority of patients (14.8% and 18.5%), and beta-blockers did not show effectiveness in patients with inducible VT and were only partially effective in patients with non-inducible VT (28%). Amiodarone was not superior to sotalol, being effective in 15.4 and 25% of the respective groups, and verapamil was more effective in non-inducible VT group (0% vs. 50%).

In contrast to the results published by Wichter, in 2009 Marcus et al[102] reported that neither beta-blockers nor sotalol seemed to be protective against clinically relevant ventricular arrhythmias. Moreover, the sotalol group was found to have a potential increased risk for significant ventricular arrhythmias or ICD therapy. However, is important to recognize that high risk patients for major arrhythmias were most likely to be on sotalol. On the other hand, amiodarone, although only received by a relatively small number of patients, had the greatest

efficacy in preventing ventricular arrhythmias. This study was done in 95 patients with ICD implantation selected from the North America ARVC Registry. These conflicting results need to be further addressed in future trials.

Non Pharmacologic Treatment
Implantable cardioverter-defibrillator (ICD)

The indications of ICD for primary prevention of SCD in ARVC/D patients have not been well established.[87,89] It represents prophylactic implantation based on a clinical profile with 1 or more identifiable risk factors for SCD. There is a consensus that high-risk patients should be considered as ICD placement candidates. Consequently, patients with episodes of sustained VT or VF (Level of Recommendation: IB), unexplained syncope, non-sustained VT on noninvasive monitoring, familial history of sudden death, extensive disease including those with LV involvement and good functional status (Level of Recommendation: IIaC)[87,89,103] are potential candidates for ICD implantation even in the absence of ventricular arrhythmias.[104,105] Additionally, patients with genotypes of ARVC/D associated with a high risk for SCD (eg, ARVC/D 5) should be considered as possible candidates for ICD therapy.[87,104] It is currently recommended that asymptomatic patients have to be managed in a case by case basis.

In 2005, Hodgkinson et al[104] identified 11 families from Newfoundland, Canada who were affected by autosomal-dominant ARVC/D5, which is related to mutation at chromosome 3-3p25 and is associated with early SCD, especially in men. 48 high risk patients were followed after ICD implantation (35 patients) (73%, 17 males and 18 females) for primary prevention and 13 patients (27%, males) for secondary prevention. Likewise, 58 matched high-risk patients without ICD were selected as a control group (32 males and 22 females). The authors reported a five-year mortality rate of 0% for males after ICD implantation compared to 28% in controls. In this study, homogeneous ARVC/D5 patients were studied in order to evaluate the real impact on mortality of ICD implantation. However, its clinical applicability may be reduced to patients with this specific genetic defect and may not be applied in practice to all patients with ARVC/D.

There are not specific prospective randomized trials for secondary prevention of SCD in an ARVC/D population, or comparing medical therapy versus ICD. Some observational studies have shown adequate ICD use for malignant ventricular arrhythmias/SCD in patients with ARVC/D.[93,104,106–110] Nevertheless, there are well-defined recommendations for ICD placement in patients who survived to a cardiac arrest due to VF, or after facing a sustained VT with hemodynamic compromise with no evidence of reversible causes (Level of Recommendation: IA).[87,88,93,110] For secondary prevention of SCD, ICD placement has improved survival compared with pharmacological options, regardless of the underlying myocardial disease.[87,89,111–114]

Corrado et al described an observational study focused in the impact of ICD therapy on SCD prevention in an ARVC/D population.[93] They followed 132 patients after successful implantation due to cardiac arrest, sustained VT with and without hemodynamic compromise, unexplained syncope and family history of SCD due to ARVC/D. During a mean follow-up of 3.3 years, they observed that 48% of the subjects received appropriate ICD intervention (rate of 15% per year) for episodes of VTs with a similar incidence of appropriate termination in patients classified by clinical presentation. The total patient survival rate of 96% in patients with ICD compared with a 72% of the projected SCD-free survival rates without the device in 3.3 years ($P < 0.001$). Significant predictors of malignant ventricular arrhythmias, such as history of cardiac arrest or VT with hemodynamic compromise (10% incidence per year despite antiarrhythmic drug), unexplained syncope (8% per year), younger age and left ventricular involvement were identified.

Bhonsale et al[115] recently published important predictors of appropriate ICD intervention in patients with ARVC/D who received ICD implantation for primary prevention of SCD, which include: proband status, the presence of NSVT, inducibility at EPS and a Holter PVC count $> 1,000/24$ hours, but only the presence of NSVT and inducibility after EPS remained significant predictors of appropriate ICD interventions on multivariable analysis. This is an important step in understanding and identifying predictor of appropriate therapy in these patients and developing risk stratification scheme in ARVC/D patients.[115]

Complications from ICD implantation

Although there is clear evidence of the benefit of ICD implantation as a secondary prevention mechanism for SCD, the devices are not free of short- and long-term complications. The variation of the myocardium structure with fibrofatty infiltration and RV endomyocardial scarring can produce difficulties in ICD lead placement, leading to inadequate sensing and procedural complications like myocardial injury or aneurysmal rupture.[22] Patients with ARVC/D who required ICD placements are usually younger compared to patients with ICD due to other diseases.[93] This situation leads to an increased lifetime risk of device-related complications, associated with implantation, leads, pulse generator and functionality,[110,116,117] as well as deleterious psychosocial effects and detriment of quality of life.[118,119] Finally, the current guidelines discourage the placement of defibrillators in patients with incessant VT, VF or with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. (Level of Recommendation: IIIC).[87]

ICD programming

The prevention of inappropriate ICD shocks in these patients could be increased by programming certain variables which include: faster ventricular-tachycardia/ventricular-fibrillation (VT/VF) thresholds and longer detection durations, activating enhanced detection criteria up to 200 bpm and deactivating sustained rate durations, activating algorithms to detect oversensing or lead problems and applying remote monitoring. Recently the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) was published which proves that a high-rate therapy (delivered at a heart rate of ≥200 bpm) and delayed ICD therapy, as compared with conventional device programming, were associated with reductions in a first occurrence of inappropriate therapy and reductions in all causes of mortality.[120] These findings may change the current practices with two new programming approaches, which minimize the overall shock burden.[121–123]

Radiofrequency ablation

Radiofrequency ablation has been reserved for patients with recurrent ventricular arrhythmias despite treatment with antiarrhythmic drugs.[124–126]

Ablation is considered a complementary therapy to ICD (Level of Recommendation: IIaC), useful for management of symptoms but may not be sufficient to prevent SCD.[87,89] There is a high rate of recurrence after endocardial ablation due to the characteristic generalized, patchy involvement of the myocardium and progressive nature of this disease.[124,125] It is worth pointing out that with newer current approaches for catheter ablation, by combining endocardial and epicardial ablation we can decrease the rate of recurrent VT. Multiple recent studies suggest that simultaneous epicardial and endocardial approaches for VT mapping and ablation are feasible and might even result in elimination of recurrent VT. This could be explained by the preferential epicardial infiltration of the disease.[127]

Surgical treatment

Surgical isolation of the RV free wall prevents the propagation of malignant arrhythmias from the RV to the LV; by performing this surgical procedure there would be less substrate for the electrical disturbance. This therapeutic approach was once an option for patients with VT refractory to antiarrhythmic medications.[128–130] However, patients were at risk of postoperative RV failure. Over the last decades, this procedure has been replaced by ICD placement, which has achieved widespread acceptance as a preventive treatment for SCD.

In patients with late complications of the disease, who develop heart failure symptoms or life threatening and untreatable VT, heart transplantation could be an option with good short and long term survival. Heart transplantation is essentially the final therapeutic option for these patients.[131]

Other Recommendations

Additionally, patients with signs of ventricular failure should be given optimal therapy for heart failure and anticoagulation should be considered in patients with atrial fibrillation, significant ventricular dilation or ventricular aneurysm.[60]

Screening for asymptomatic family members

Once the diagnosis of ARVC/D has been confirmed, a systematic evaluation of the family members favors an early diagnosis of possible affected subjects.

Nava et al evaluated 365 subjects from 37 Italian families affected by ARVC/D. They found that 41% (151 subjects) of the family members were affected by the disease, with clinical manifestations present during the adolescence and young adulthood.[78] They also observed a broad clinical spectrum of manifestations with incomplete expression and progressive natural history of the disease, recommending a long-term follow up of relatives. Family members who remain asymptomatic in the early "concealed" phase could still be at risk of disease progression and/or adverse cardiovascular events.[72]

In 2010, Marcus et al proposed a modification of the 1994 Task Force Criteria in order to improve the diagnostic sensitivity for early and familiar involvement,[72] incorporating evidence available from genetics and technologic advances, including improvement of echocardiographic techniques and CMR. As part of the evaluation, an ECG, 24 hour Holter monitoring, echocardiogram and, if possible, a signal averaged ECG should be obtained on all first-degree relatives of patients diagnosed with ARVC/D. Family involvement is considered if there is evidence of ECG changes including T wave inversions in V1–V3 (individuals older than 14 years in the absence of RBBB), late potentials on SAECG, episodes of VT with RV origin pattern or more than 200 premature ventricular contractions in 24 hours, as well as the RV structural or functional abnormalities previously described.[72,86]

Quarta et al evaluated the roll of mutation analysis on familial evaluation with ARVC/D.[132] The study enrolled 210 first-degree relatives and 49 living probands from 100 affected families. Data obtained from clinical assessment and screening of 5 desmosomal genes associated with the disease showed clinical expression in 41.9% of relatives, at least 1 mutation in 56 families and multiple desmosomal variants in 8 families. Multiple mutations were more common in probands than in relatives, and they were associated with a significant increase in risk of disease expression (ie, 5-fold in affected family members). On the other hand, the prevalence of the disease in affected first-degree relatives was similar after comparing probands with positive and negative mutation screening (28.9% vs. 20%, respectively; $P = 0.57$), suggesting possible non-identified genetic abnormalities.[132]

Although genetic analysis in not considered a contributor to risk stratification, it could be useful in families with history of SCD. Identification of pathogenic mutations in affected patients with cascade screening of relatives may offer an alternative cardiovascular evaluation of family members. Therefore, genetic counseling may be provided, assessing hereditary risks to next generations.[72,89,132]

Conclusion

ARVC/D is a progressive disease with life-threatening complications, which constitute a clinical diagnostic challenge for physicians, given the different genotypic and phenotypic variations and the wide ranges of clinical manifestations. The main challenge is to improve the risk stratification for better identification of high risk patients of SCD and heart failure, who most benefit from early intervention with lifestyle changes, restriction of physical activity, antiarrhythmic drugs, ICD placement, new ablation approaches with simultaneous endocardial and epicardial ablation and, if necessary, heart transplantation. These interventions are available and life saving, with the potential to change the natural history of the disease by offering a good quality and better life expectancy.

Author Contributions
Conceived and designed the review article: JR. Analyzed the data: EM, CM. Wrote the first draft of the manuscript: EM, CM. Contributed to the writing of the manuscript: RL. Agree with manuscript results and conclusions: JR. Jointly developed the structure and arguments for the paper: EM. Made critical revisions and approved final version: JR, EM, CM. All authors reviewed and approved of the final manuscript

Competing Interests
Author(s) disclose no potential conflicts of interest.

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