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# Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/65316>

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## Abstract

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare disease characterized by progressive fibrofatty replacement of the myocardium, primarily involving the right ventricle (RV). The structural changes in the ventricular myocardium form a substrate for ventricular arrhythmia ranging from premature ventricular complexes to ventricular tachycardia typically of RV origin and may result in RV failure and progress to congestive heart failure at a later stage. ARVC/D is a recognized cause of sudden cardiac death in young people, but it may occur at any age. With the discovery of underlying pathogenic mutations involved in the disease development and insight from long-term follow-up of ARVC/D patients, ARVC/D is an inherited cardiomyopathy. Mutations in at least eight genes have been involved in ARVC/D genesis in 30–50% of patients. Most of these genes are involved in the function of desmosomes, which are structures that attach heart muscle cells to one another. Desmosomes provide strength to the myocardium and play a role in signaling between neighboring cells. Mutations in the genes responsible for ARVC/D often impair the normal desmosomal function. There has been significant advancement in the diagnosis and management of ARVC/D in the past few decades. This chapter provides an overview of ARVC/D pathophysiology, clinical presentations, diagnosis, and management.

**Keywords:** cardiomyopathy, arrhythmia, right ventricle, sudden cardiac death, heart failure

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## 1. Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare disease characterized by progressive fibrofatty replacement of the myocardium, primarily involving the right ventricle (RV) [1–4].

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The typical age of presentation is between the second and the fourth decade of life. The structural changes in the ventricular myocardium form a substrate for ventricular arrhythmia ranging from premature ventricular complexes (PVCs) to ventricular tachycardia (VT), typically of RV origin and may result in RV failure, and progress to congestive heart failure at a later stage. ARVC/D is a recognized cause of sudden cardiac death (SCD) in young individuals, but it may occur at any age [4].

ARVC/D was first described by Frank et al. [1], and the first clinical profile of the disease was published in 1982 [2]. It was described as a disease in which “the right ventricular musculature is partially or totally absent and is replaced by fatty and fibrous tissue [2].” With the discovery of underlying pathogenic mutations involved in the disease development and insight from long-term follow-up of ARVC/D patients, the ARVC/D is currently considered to be an inherited cardiomyopathy [4–6]. However, the presence of sporadic cases of ARVC/D increased the possibility of nongenetic causes.

Mutations in at least eight genes have been involved in the ARVC/D genesis in 30–50% patients. Most of these genes are involved in the function of desmosomes, which are structures that attach heart muscle to one another. Desmosomes provide strength to the myocardium and also play a role in signaling between neighboring cells. Mutations in the genes responsible for ARVC/D often impair the normal desmosomal function. This results in cells of the myocardium detaching from one another and dying (apoptosis). They are then replaced with fibrous and fibrofatty tissue. The apoptosis occurs predominantly when the heart muscle is placed under stress (such as during vigorous exercise). Most of these genes code for desmosome proteins—plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP2), the desmoglein-2 (DSG2), and desmocollin-2 (DSC2)—and other genes that code for nondesmosomal protein (e.g., RYR2 and TMEM43) have also been associated with ARVC/D [7]. Additionally, an autosomal recessive variant of ARVC/D has been described. The first disease-causing gene, encoding the desmosomal protein plakoglobin (JUP), was identified in patients with Naxos disease and is an autosomal recessive variant of ARVC/D. It was first reported from the Greek island of Naxos and is associated with palmoplantar keratoderma and woolly hair [8]. Another recessive mutation of DSP has been reported and associated with Carvajal syndrome, another cardiovascular disease [9].

In the past few decades, there has been a significant improvement in our understanding of this disease pathogenesis, natural course, diagnosis, and management.

This chapter provides an overview of ARVC/D pathophysiology, clinical presentations, diagnosis, and management.

## 2. Epidemiology

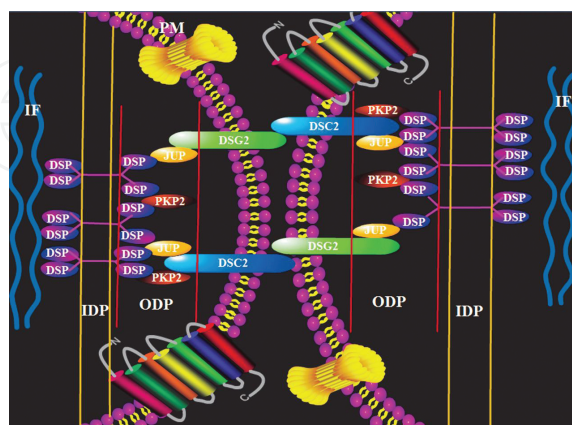
The estimated prevalence of ARVC/D in the general population ranges from 1 in 2000 to 1 in 5000 individuals; men are more frequently affected than women, with an approximate ratio of 3:1 [10, 11].

The median age at onset of the disease is about 30 years, whereas it rarely manifests before the age of 12 or after the age of 60 years [12, 13]. ARVC/D is a leading cause of sudden cardiac death (SCD) accounting for 11–22% of cases of SCD in the young athlete patient population [13–15]. However, this varies based on the geographic area as it accounts for approximately 22% of SCD cases in athletes in northern Italy [5] and about 17% of SCD in young people in the United States [16]. The genes involved and different mode of inheritance may explain the ARVC/D ethnic variations [17]. The most prevalent mode of inheritance of ARVC/D is an autosomal dominant; however, autosomal recessive form has also been described such as Naxos disease. This disease was first described in Naxos Island, Greece, and it is associated with cutaneous manifestations such as palmoplantar keratosis [8]. Although there are no genetic studies in ARVC/D Chinese patients, some studies showed a lower familial incidence of premature SCD among these patients [18].

### 3. Molecular genetics

ARVC/D is a genetically determined cardiac disease because one or more first-degree relatives also display signs of the disease in 30–50% of cases [2, 19].

A large majority of mutations in ARVC/D patients have been found in genes encoding different components of the cardiac desmosome, i.e., plakophilin 2 (PKP2), desmocollin 2 (DSC2), desmoglein 2 (DSG2), desmoplakin (DSP), and plakoglobin (JUP), suggesting that ARVC/D is primarily a disease of disturbed desmosomal function. However, mutations in other genes (nondesmosomal genes) have also been reported in ARVC/D, including transmembrane protein 43 (TMEM43), desmin (DES), and titin (TTN), indicating genetic heterogeneity. Several ARVC/D cases were found to be caused by multiple mutations in the same gene (compound heterozygosity) or mutations in different genes (digenic inheritance), which could result in an earlier onset and increased disease severity [7] (**Figure 1**).



**Figure 1.** The structural schematic diagram of desmosome. IDP, inner dense plaque; ODP, outer dense plaque; PM, plasma membrane; DSG2, desmoglein-2; DSC2, desmocollin-2; JUP, plakoglobin; PKP2, plakophilin-2; DSP, desmoplakin; IF, intermediate filaments. Adapted with permission from Que et al. [186].

The ARVC/D is inherited predominantly as an autosomal dominant (the classical form), and as autosomal recessive (nonclassical form) such as Naxos disease and Carvajal syndrome [8, 9].

**Table 1** summarizes ARVC/D genes and corresponding phenotypes.

ARVC/D subtype	Location (chromosome/locus)	Inheritance	Gene/locus (encoded protein)
ARVC/D 1	14q24.3	AD	TGFβ3
ARVC/D 2	1q43	AD	RyR2
ARVC/D 3	14q12-q22	AD	–
ARVC/D 4	2q32.1-q32.3	AD	–
ARVC/D 5	3p25.1	AD	TMEM43
ARVC/D 6	10p14-p12	–	–
ARVC/D 7	10q22.3	AD	DES
ARVC/D 8	6p24.3	AD	DSP
ARVC/D 9	12p11.21	AD	PKP2
ARVC/D 10	18q12.1	AD	DSG2
ARVC/D 11	18q12.1	AR/AD	DSC2
ARVC/D 12	17q21.2	AD	JUP
Naxos disease	17q21.2	AR	JUP
ARVC/D 13	10q21.3	AD	CTNNA3

**Abbreviations:** AD: autosomal-dominant; AR: autosomal-recessive; ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia; CTNNA3: catenin Alpha; DSC2: desmocollin-2; DSG2: desmoglein-2; DES: desmin; DSP: desmoplakin; JUP: junction plakoglobin; PKP2: plakophilin-2; RyR2: Ryanodine receptor 2; TGF: transforming growth factor; TMEM43: transmembrane protein 43.

**Table 1.** Arrhythmogenic ventricular cardiomyopathy/dysplasia genetics from OMIM®and Online Mendelian Inheritance in Man®.

3.1. Desmosomal ARVC/D

3.1.1. Autosomal dominant disease

3.1.1.1. Plakophilin-2

Plakophilin-2 is a protein that in humans is encoded by the PKP2 gene [20]. Plakophilin 2 is expressed in cardiac muscle as well as skin, where it functions to link cadherins to intermediate filaments in the cytoskeleton. In cardiac muscle, plakophilin-2 is found in desmosome structures located within intercalated discs [21]. In 2004, Syrris et al. [22] was the first to show that mutations in PKP2 are a major cause of ARVC/D. The disease was incompletely penetrant in most mutation carriers as confirmed by subsequent studies [23–26]. It is estimated that up to 70% of all mutations associated with ARVC/D are within the PKP2 gene [27, 28]. This finding is consistent with this chapter author's experience of ARVC/D patients in Saudi Arabia [29]. Specific and sensitive markers of PKP2 and plakoglobin mutation carriers in ARVC/D have been identified to include T-wave inversions, right ventricular wall motion abnormalities, and

ventricular extrasystoles [30]. Investigations looking at the clinical and genetic characterization of ARVC/D to understand the penetrance associated with PKP2 mutations, as well as other genes encoding desmosomal proteins, in disease progression and outcome, are of major interest [31–40]. PKP2 mutations were also found to coexist with sodium channelopathies in patients with Brugada syndrome [41, 42].

#### 3.1.1.2. *Desmoplakin*

Desmoplakin is a protein in humans that is encoded by the DSP gene [43, 44]. Desmoplakin is a critical component of desmosome structures in cardiac muscle and epidermal cells, which function to maintain the structural integrity at adjacent cell contacts. In cardiac muscle, desmoplakin is localized to intercalated discs, which mechanically couple cardiac cells to function in a coordinated syncytial structure. Mutations in this gene are the cause of several cardiomyopathies, including dilated cardiomyopathy (DCM) [9, 45], and ARVC/D [46–50]. Mutations in DSP have also been associated with striate palmoplantar keratoderma [9, 48, 51]. Carvajal syndrome results from an autosomal recessive mutation in DSP gene [45] (see below).

#### 3.1.1.3. *Desmoglein-2*

Desmoglein-2 is a protein that in humans is encoded by the DSG2 gene [52]. Desmoglein-2 is highly expressed in cardiomyocytes and epithelial cells. Desmoglein-2 is localized to desmosome structures at regions of cell-cell contact and functions to structurally adhere adjacent cells together. In cardiac muscle, these regions are specialized regions known as intercalated discs. Mutations in desmoglein-2 have been associated with ARVC/D [53] and familial dilated cardiomyopathy [54].

#### 3.1.1.4. *Desmocollin-2*

Desmocollin-2 is a protein that in humans is encoded by the DSC2 gene [55]. Desmocollin-2 is a cadherin-type protein that functions to link adjacent cells together in desmosomes. Desmocollin-2 is widely expressed and is the only desmocollin isoform expressed in cardiac muscle, where it localizes to intercalated discs. Mutations in DSC2 have been causally linked to ARVC/D.

Syrri et al. [56] reported 4 DSC2 mutations in 77 probands who were negative for other mutations. Disease expression was variable, and most mutation carriers had LV involvement. Other studies show the same findings [33, 34, 57, 58].

#### 3.1.1.5. *Plakoglobin*

The first dominant mutation in plakoglobin was described in a German family [59]. Affected individuals carried an insertion of an extra serine residue at position 39 in the N-terminus of plakoglobin (S39\_K40insS) [59]. None of the individuals affected by the S39\_K40insS mutation showed apparent cutaneous abnormalities, in contrast to abnormalities seen in patients with Naxos disease.

### 3.1.2. Autosomal recessive

#### 3.1.2.1. Plakoglobin

Plakoglobin, also known as junction plakoglobin or gamma-catenin, is a protein that in humans is encoded by the JUP gene. Plakoglobin is a cytoplasmic component of desmosomes and adherens junctions structures located within intercalated discs of cardiac muscle that function to anchor sarcomeres and join adjacent cells in cardiac muscle. It is the first gene that was identified as a cause of ARVC/D by Protonotarios et al. [60] in 1986. The mutations in JUP specifically cause an autosomal recessive form of the disease referred to as Naxos disease. It was first described in patients originating from the Hellenic island of Naxos. Naxos disease is characterized phenotypically by cutaneous manifestations such as wooly hair plus palmar and plantar erythema that progresses to keratosis with physical activity involving the palms and soles of the feet [7, 36–38, 61–63]. Noninvasive cardiac screening identified T-wave inversion, abnormalities in RV wall motion, and frequent ventricular extrasystoles as sensitive and specific markers of a JUP mutation [30].

#### 3.1.2.2 Desmoplakin

Carvajal syndrome is a variety of Naxos disease presenting at a younger age with more pronounced left ventricular involvement has been described in families from India and Ecuador [34, 35, 45, 64]. It results from an autosomal recessive mutation of a frameshift (7901delG) in DSP that results in a combination of above conditions, including dilated cardiomyopathy, keratoderma, and wooly hair [45]

## 3.2. Nondesmosomal ARVC/D

### 3.2.1. Cardiac ryanodine receptor (RyR2)

The RyR2 receptor is responsible for calcium release from the sarcoplasmic reticulum. Mutations in the cardiac ryanodine receptor RyR2 have been described in only one Italian ARVC/D family [65].

Mutations in the human RYR2 gene have been associated with three inherited cardiac diseases: arrhythmogenic right ventricular cardiomyopathy type 2 (ARVC/D2) [65, 66], catecholaminergic polymorphic ventricular tachycardia (CPVT) [67, 68], and familial polymorphic ventricular tachycardia (FPVT) [69, 70].

### 3.2.2. Transforming growth factor beta-3 (TGFβ3)

The TGF-β superfamily of cytokines consists of proteins that regulate different physiological processes, such as embryonic development, chemotaxis, homeostasis, cell cycle control, and wound healing [71]. The gene has been mapped to chromosome 14. With the screening of the promoter and untranslated regions, a mutation of the TGFβ3 gene was found in all clinically affected members of a large family with ARVC/D [72]. TGFβs stimulate mesenchymal cells to

proliferate and to produce extracellular matrix components [73]. It is, therefore, possible that enhanced TGF $\beta$ 3 activity can lead to myocardial fibrosis.

### 3.2.3. Transmembrane protein 43 (TMEM43)

Transmembrane protein 43 (also called luma) is a protein that is encoded by the TMEM43 gene in humans [74]. TMEM43 may have an important role in maintaining a nuclear envelope structure by organizing protein complexes at the inner nuclear membrane.

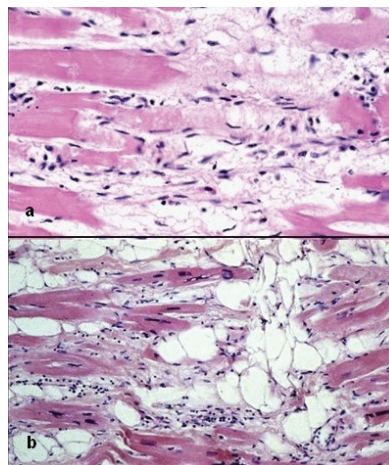
A high-risk form of ARVC/D with a fully penetrant, and sex influenced inheritance has been identified in 15 unrelated families in a genetically isolated population in Newfoundland, Canada. The underlying mutation for this form of the disease was a missense mutation in the TMEM43 gene [75]. The TMEM43 gene contains the response element for PPAR gamma, which is an adipogenic transcription factor. The dysregulation of the adipogenic pathway regulated by PPAR gamma as a result of TMEM43 gene mutation may explain the fibrofatty replacement of myocardium in patients with ARVC/D [75]. Several other studies also show that mutations in TMEM43 are associated with ARCV/D [75–78].

### 3.2.4. Others

Only isolated reports showed causal mutations in other nondesmosomal genes, such as desmin (DES), titin (TTN), Lamin A/C (LMNA), phospholamban (PLN) and  $\alpha$ T-catenin (CTNNA3), sometimes with a clinical phenotype similar but not identical to ARVC/D, as to be considered phenocopies or overlap syndromes [79].

## 4. Pathophysiology

The structural abnormalities in ARVC/D result from the fibrofatty infiltration of the RV myocardium, which leads to progressive RV dilatation and dysfunction (**Figure 2**). The gross



**Figure 2.** Typical histological features of ARVC/D. (a) Ongoing myocyte death and (b) early fibrosis and adipocytes infiltration. Adapted with permission from Thiene et al. [187].

pathognomonic features of ARVC/D consist of RV aneurysms, whether single or multiple, located in the so-called “triangle of dysplasia” which involve RV inflow, apex and outflow tract [4]. The left ventricle (LV) is less commonly involved, and the septum is relatively spared.

#### 4.1. Early hypothesis

Basso et al. [4] suggested that the mechanism for myocardial loss and myocardial atrophy appeared to be the consequence of acquired injury (myocyte death) and repair (fibrofatty replacement), mediated by patchy myocarditis. The presence of apoptosis (programmed cell death) is confirmed in ARVC/D [80]. Inflammation, enhanced fibrosis, and loss of function are based on pathological reports of inflammatory infiltrates detected in the heart specimen collected from ARVC/D patients [81]. More recent studies showed that myocarditis might mimic ARVC/D, or it may be superimposed on existing disease in the affected heart muscle [82]. Another proposed mechanism was transdifferentiation of myocardium. This hypothesis assumes that myocardial cells can change from cardiac muscle to adipose tissue [83]. However, it was based on an observation in one patient only.

#### 4.2. Current hypothesis

##### 4.2.1. Abnormal cell-cell adhesion (desmosomal disease)

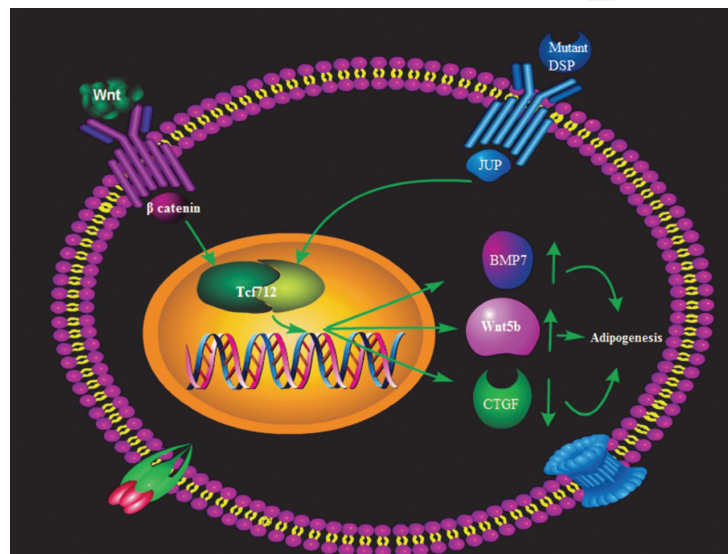
Our current understanding of ARVC/D indicates that it is a desmosomal disease. Desmosomes mediate cell-cell adhesion and provide cells with mechanical strength [84, 85]. They are present in tissues with mechanical stress like myocardium and epidermis. Desmosomes consist of three families of proteins: the armadillo proteins (junction plakoglobin and plakophilin), cadherins (desmocollins and desmogleins), and plakins (desmoplakin) [86]. Electron microscopy studies have demonstrated intercalated disc remodeling, which raised the hypothesis of an abnormal cell-cell adhesion in disease pathogenesis even before the discovery of desmosomal genes in ARVC/D [87, 88]. Reduced cell-cell adhesion was demonstrated using monolayers of neonatal rat ventricular myocytes in which PKP2 was silenced and subjected to a defined mechanical intervention [89]. However, when expressing mutant forms of either PKP2 or JUP, cells exhibited abnormal signaling in response to mechanical stress, but showed a preserved intercellular adhesion, which raised a question mark about the primary role of cell-cell adhesion in ARVC/D pathogenesis [90]. At the same time, the reduced junctional signal for JUP appears to have a significant role in the disease pathogenesis as demonstrated by Asimaki et al. [91] in myocardial samples from ARVC/D patients. This may indicate a possible role of intracellular signaling rather than adhesion, as suggested by other groups [92, 93].

##### 4.2.2. Abnormal intercellular junction proteins and intracellular signaling

Suppression of the canonical Wnt/ $\beta$ -catenin signaling pathway is another proposed mechanism in the pathogenesis of ARVC/D. Plakoglobin ( $\gamma$ -catenin), a protein with functional similarities to catenin, can localize both to the plasma membrane and the nucleus [94]. Garcia-Gras et al. [92] demonstrated that disruption of desmoplakin frees plakoglobin from the plasma membrane allowing it to translocate to the nucleus and suppress canonical Wnt/ $\beta$ -catenin

signaling. Wnt/ $\beta$ -catenin signaling can inhibit adipogenesis by preventing mesodermal precursors from differentiating into adipocytes [95]. Suppression of Wnt/ $\beta$ -catenin signaling by plakoglobin nuclear localization could, therefore, promote the differentiation of adipose tissue in the cardiac myocardium in patients with ARVC/D [92] (**Figure 3**).

Recently, the Hippo/YAP signaling pathway has been associated with ARVC/D pathogenesis. The YAP interacts with  $\beta$ -catenin to drive Wnt-related gene expression in the nucleus. Chen et al. [96] demonstrated aberrant activation of the Hippo kinase cascade resulting in phosphorylation and cytoplasmic retention of YAP in ARVC/D myocardial samples, mouse models and pkp2 knockdown HL-1 myocytes.



**Figure 3.** The suppression of the Wnt/ $\beta$ -catenin signal pathway. Mutant DSP frees JUP from the plasma membrane, allowing it to translocate to the nucleus. Nucleus location of JUP might be the initiator of the suppression of Wnt signaling. Plakoglobin competes against  $\beta$ -catenin for binding with Tcf712 (transcriptional factor 712), further leading to a series of consequences, increased expression of BMP7 and noncanonical Wnt5b and reduction of CTGF. Bone morphogenic protein 7 and Wnt5b are well-known promoters of adipogenesis as opposed to CTGF, which is inhibitor of adipogenesis. Ultimately, the pathological morphology of ARVC/D developed. Adapted with permission from Que et al. [186].

#### 4.2.3. Gap junction and ion channel remodeling

At the cellular level, the functional triad of desmosomes, gap junctions and sodium channels is essential for normal function. The change in the composition of one component of this triad may affect the function and integrity of the others [97]. Impairment in mechanical coupling as expressed with diminished expression of connexin-43 at the intercellular junction was demonstrated in most of ARVC/D cases [98, 99].

Furthermore, in the ARVC/D experimental model, reduced cardiac sodium current was found [100–104]. These findings led researchers to hypothesize that life-threatening ventricular arrhythmias could occur in patients with ARVC/D even preceding the structural abnormalities due to electrical uncoupling and reduced sodium current, but this has yet to be proven.

Furthermore, animal studies using high-throughput drug screening identified as SB216763 showed an ability to restore the subcellular distribution of JUP, connexin-43 and Nav1.5 and of SAP97, a protein known to mediate the forward trafficking of Nav1.5 and Kir2.1. The SB216763 is already known as an activator of the canonical Wnt signaling pathway. This might be the beginning to move from experimental models to a target gene therapy [104].

## 5. Clinical presentation

In its initially described classical form of ARVC/D, the RV is primarily affected with possible LV involvement in a later stage. However, two additional patterns of disease have been identified by clinicogenetic characterization of families. These are the left dominant phenotype, with early and predominant LV manifestations, and the biventricular phenotype with equal involvement of both ventricles. Immunohistochemical studies at a molecular level indicated that ARVC/D is a global biventricular disease [95]. However, histologically and functionally overt manifestations of the disease usually start in the RV. There is no clear explanation for this finding, but the possible mechanism is that RV is less able to withstand pressure (over)load in the presence of impaired function of mechanical junctions due to their thin wall. The rare variant of the disease with cutaneous manifestations (palmoplantar keratoderma and wooly hair) has its features that will be discussed briefly later on.

### 5.1. Classic form of ARVC/D

ARVC/D patients typically present with monomorphic VT originating from the RV. However, rarely, sudden death at young age, or RV failure may be the first presentation. Patients' symptoms may include palpitations, shortness of breath, dizziness, and syncope or near syncope. Based on clinicopathologic and patients' follow-up studies, four different disease phases have been described for the classical form of ARVC/D, i.e., primarily affecting the RV (Table 2):

1. Concealed phase or early ARVC/D is characterized by the absence of obvious clinical changes, however, subtle RV structural changes may be found. Generally, these patients are asymptomatic but still at risk of SCD especially during heavy exercise.
2. The overt phase of the disease is characterized by the presence of patient's symptoms such as palpitations, syncope and ventricular arrhythmias ranging from isolated PVCs to sustained VT and ventricular fibrillation (VF).
3. The third phase is characterized by RV failure as manifest by RV dilatation and the reduced RV systolic function due to progressive loss of myocardium, with the preserved LV function.
4. Biventricular failure phase is characterized by LV involvement, which usually occurs at a late stage. This phase may mimic DCM and may require cardiac transplantation.

Phase	Characteristics
<b>Concealed</b>	No symptoms Subtle structural changes
<b>Overt</b>	Ventricular arrhythmias (PVCs/VT of LBBB morphology) RV structural abnormalities
<b>RV failure</b>	Symptoms and signs of RV failure Preserved LV function
<b>Biventricular failure</b>	Symptoms and signs of LV failure LV structural changes

**Table 2.** Clinicopathologic phases of ARVC/D.

## 5.2. Nonclassic form of ARVC/D

### 5.2.1. ARVC/D with cutaneous manifestations (cardiocutaneous disease)

#### 5.2.1.1. Naxos disease

Naxos disease is a recessively inherited stereotype association of arrhythmogenic cardiomyopathy with a cutaneous phenotype, characterized by peculiar wooly hair and palmoplantar keratoderma [60]. It is a homozygous recessive JUP mutation. The cardiac manifestations of the disease are identical to ARVC/D in both clinical and histological studies [5, 105]. Since 1995, according to the classification of World Health Organization, Naxos disease has been considered as the recessive form of ARVC/D [106].

As mentioned earlier, the disease was first described by Protonotarios et al. [60] in families originating from the Greek island of Naxos. Later on the affected families were detected in other Greek Aegean islands, and other countries [106–108]. The typical clinical presentation of the disease includes appearance of wooly hair appears from birth, whereas palmoplantar keratoderma develops during the first year of life when infants start to use their hands and feet [109]. The cardiomyopathy clinically manifests by adolescence and shows 100% penetrance [110]. Patients with Naxos disease is typically present with syncope and/or ventricular tachycardia of LBBB configuration. As with classic ARVC/D, sudden death may be the first manifestation of the disease. About one-third of patients become symptomatic before the 30th year of life, and a few clinical findings of an early heart disease can be detected during childhood in some cases [108]. They have ECG abnormalities, RV structural alterations, and LV involvement. In one series of 26 patients followed for 10 years, 62% had structural progression of RV abnormalities and 27% developed heart failure due to LV involvement [110]. Naxos ARVC/D is a rather progressive heart disease with adverse prognosis, especially in young. The annual disease-related and sudden death mortality have been estimated at 3% and 2.3%, respectively [110]. The risk factors for sudden death based on a long-term study of an unselected population of patients with Naxos disease include the history of syncope, the appearance of symptoms and severely progressed disease to the right ventricle before the age of 35 years, and the involvement of the left ventricle [110].

#### 5.2.1.2. *Carvajal syndrome*

Carvajal syndrome with the same cutaneous manifestations as Naxos disease but with predominantly LV involvement has been described in families from India and Ecuador [45, 111]. It is associated with a DSP gene mutation and is also a recessive disease. The cardiomyopathy is clinically manifested during childhood leading more frequently to a dilated cardiomyopathy and heart failure. In Carvajal syndrome, the heart disease is clinically manifested earlier during childhood [45, 111]. A significant proportion of patients developed heart failure at an early stage of the disease, and most of them died during adolescence. In a single case, gross cardiac pathologic examination showed aneurysms of the RV outflow tract, apex and posterior wall and involvement of the LV. In histologic examination, findings similar to ARVC/D pathology were found with areas of extensive myocardial loss and replacement fibrosis, particularly in subepicardial layers; however, there was no fatty infiltration [112].

#### 5.2.2. *Left-dominant arrhythmogenic cardiomyopathy (LDAC)*

Patients with LDAC (also may refer to as left-sided ARVC/D or arrhythmogenic left ventricular cardiomyopathy) have fibrofatty changes, which predominantly involve the LV [113–117]. LDAC is characterized by ECG changes in the form of (infero)lateral T-wave inversion, arrhythmias of the LV origin. ARVC/D is distinguished from DCM by a propensity towards arrhythmia exceeding the degree of ventricular dysfunction [117]. Patients with LDAC may present with arrhythmias or chest pain, shortness of breath, syncope or presyncope at ages ranging from adolescence to over 80 years. In cardiac MRI, about one-third of patients show an LV ejection fraction less than 50% [117]. Furthermore, MRI with late gadolinium enhancement (LGE) of the LV demonstrated late enhancement extending through the outer one-third of the LV myocardium to the right side of the septum [117]. Some patients with LDAC have desmosomal gene mutations similar to ARVC/D (desmoplakin, plakophilin-2, and desmoglein-2) [64].

## 6. Diagnosis

The diagnosis of ARVC/D might be challenging in patients with early stages of the disease. The establishment of ARVC/D Task Force diagnostic criteria in 1994 and its modification in 2010 have improved the clinical diagnosis of the disease [118, 119]. The current Task Force criteria are the essential standard for classification of individuals suspected of ARVC/D. The Task Force criteria included six different categories: (1) global and regional dysfunction and structural alterations, (2) tissue characterization, (3) depolarization abnormalities, (4) repolarization abnormalities, (5) arrhythmias, and (6) family history, including pathogenic mutations. The diagnostic criteria within each category are further classified as major or minor according to their specificity for the disease. To fulfill ARVC/D diagnosis, it is required to have either two major or one major plus two minor or four minor criteria. The diagnosis of ARVC/D is regarded as definite with two major or one major and two minor criteria or four minor criteria from different categories; borderline with one major and one minor or three minor

criteria from different categories; and possible with one major or two minor criteria from different categories. **Table 3** presents an overview of the 2010 modified Task Force criteria.

The Revised Task Force Criteria for ARVC/D	
I. Global or regional dysfunction and structural alterations <sup>1</sup>	
Major	Minor
By 2D echo: <ul style="list-style-type: none"><li>• Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole):  -PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m<sup>2</sup>) -PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m<sup>2</sup>) or -fractional area change ≤33%</li></ul> By MRI: <ul style="list-style-type: none"><li>• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:  -Ratio of RV end-diastolic volume to BSA ≥110 mL/m<sup>2</sup> (male) or ≥100 mL/m<sup>2</sup> (female) or -RV ejection fraction ≤40%</li></ul> By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm	By 2D echo: <ul style="list-style-type: none"><li>• Regional RV akinesia or dyskinesia and 1 of the following (end diastole):  -PLAX RVOT ≥29 to &lt;32 mm (corrected for body size [PLAX/BSA] ≥16 to &lt;19 mm/m<sup>2</sup>) -PSAX RVOT ≥32 to &lt;36 mm (corrected for body size [PSAX/BSA] ≥18 to &lt;21 mm/m<sup>2</sup>) or -fractional area change &gt;33% to ≤40%</li></ul> By MRI: <ul style="list-style-type: none"><li>• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:  -Ratio of RV end-diastolic volume to BSA ≥100 to &lt;110 mL/m<sup>2</sup> (male) or ≥90 to &lt;100 mL/m<sup>2</sup> (female) or -RV ejection fraction &gt;40% to ≤45%</li></ul>
II. Tissue characterization of wall	
Major	Minor
<ul style="list-style-type: none"><li>• Residual myocytes&lt;60% by morphometric analysis (or &lt;50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement</li></ul>	<ul style="list-style-type: none"><li>• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy</li></ul>

of tissue on endomyocardial biopsy

### III. Repolarization abnormalities

Major	Minor
<ul style="list-style-type: none"> <li>Inverted T waves in right precordial leads (<math>V_1</math>, <math>V_2</math>, and <math>V_3</math>) or beyond in individuals &gt;14 years of age (in the absence of complete right bundle-branch block QRS <math>\geq 120</math> ms)</li> </ul>	<ul style="list-style-type: none"> <li>Inverted T waves in leads <math>V_1</math> and <math>V_2</math> in individuals &gt;14 years of age (in the absence of complete right bundle-branch block) or in <math>V_4</math>, <math>V_5</math>, or <math>V_6</math></li> <li>Inverted T waves in leads <math>V_1</math>, <math>V_2</math>, <math>V_3</math>, and <math>V_4</math> in individuals &gt;14 years of age in the presence of complete right bundle-branch block</li> </ul>

### IV. Depolarization/conduction abnormalities

Major	Minor
<ul style="list-style-type: none"> <li>Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (<math>V_1</math> to <math>V_3</math>)</li> </ul>	<ul style="list-style-type: none"> <li>Late potentials by SAECG in <math>\geq 1</math> of 3 parameters in the absence of a QRS duration of <math>\geq 110</math> ms on the standard ECG</li> <li>Filtered QRS duration (fQRS) <math>\geq 114</math> ms</li> <li>Duration of terminal QRS <math>&lt; 40</math> <math>\mu V</math> (low-amplitude signal duration) <math>\geq 38</math> ms</li> <li>Root-mean-square voltage of terminal 40 ms <math>\leq 20</math> <math>\mu V</math></li> <li>Terminal activation duration of QRS <math>\geq 55</math> ms measured from the nadir of the S wave to the end of the QRS, including R', in <math>V_1</math>, <math>V_2</math>, or <math>V_3</math>, in the absence of complete right bundle-branch block</li> </ul>

### V. Arrhythmias

Major	Minor
<ul style="list-style-type: none"> <li><b>Nonsustained</b> 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)</li> </ul>	<ul style="list-style-type: none"> <li>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</li> <li>&gt;500 ventricular extrasystoles per 24 hours (Holter)</li> </ul>

### VI. Family history

Major	Minor
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- ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
- ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
- Identification of a pathogenic mutation<sup>2</sup> categorized as associated or probably associated with ARVC/D in the patient under evaluation
- **Abbreviations:** PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.
- **Diagnostic terminology for original criteria:** This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

<sup>1</sup> Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

<sup>2</sup> A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. Modified from Marcus FI et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121(13):1533-41. DOI:10.1161/CIRCULATIONAHA.108.840827. *Eur Heart J*. 2010 Apr;31(7):806-14. DOI:10.1093/eurheartj/ehq025.)

**Table 3.** The 2010 revised Task Force criteria for the diagnosis of ARVC/D.

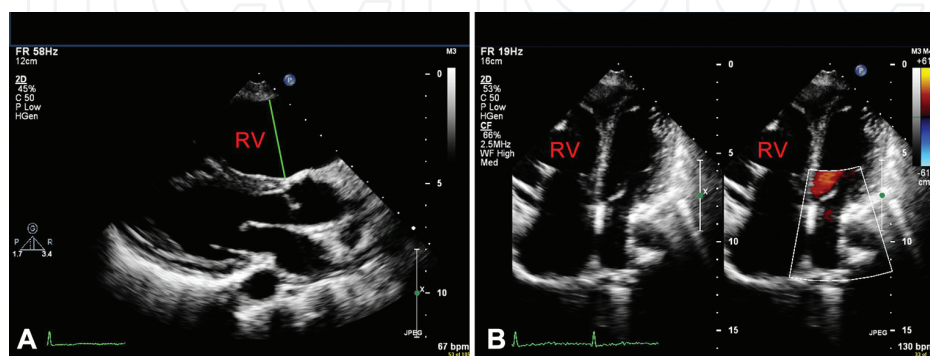
Evaluation of patients with suspected ARVC/D should include: a detailed medical history including a detailed family history, physical examination, 12-lead electrocardiogram (ECG), signal-averaged ECG (SAECG), 24-hours Holter monitoring, exercise testing, echocardiography (including RV functional evaluation and quantitative wall motion analysis), and when appropriate a more detailed analysis of the RV function by cardiac magnetic resonance imaging (MRI). Invasive tests with RV endomyocardial biopsy and RV angiogram are also useful for diagnostic purposes. Electrophysiology studies might be helpful in the evaluation of the VT site of origin and ablation of VT when indicated.

A brief description of diagnostic tests based on the Task Force criteria will be outlined below.

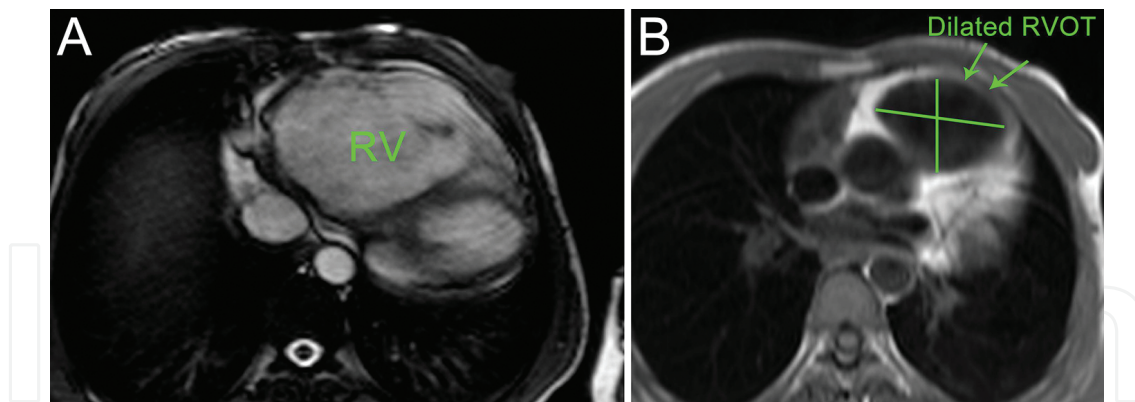
### 6.1. Global and regional dysfunction and structural alterations

Various imaging modalities have been used to evaluate RV (and LV) size and function, including echocardiography, cardiac MRI, computed tomography scan (CT scan) and/or RV

angiography. According to the Task Force criteria, major criteria are defined as the presence of akinetic or dyskinetic areas in the RV combined with severe dilatation of the RV or RV ejection fraction 40% or lower [119]. In RV angiography the finding of only regional akinesia, dyskinesia or an aneurysm is considered to be sufficient for qualification as a major criterion. RV angiography has historically been considered the most sensitive method to visualize RV structural abnormalities, with a high specificity of 90% [120]. Compared to angiography, echocardiography is noninvasive, widely available, low in cost, and easy to perform and interpret, and has played a crucial role in imaging structural and functional abnormalities of the RV (**Figure 4**). It serves as the first-line imaging technique for evaluating patients suspected of ARVC/D and in family screening. There are numerous reports of the use of echocardiography to aid in the diagnosis of ARVC/D. These studies have found that the presence of right ventricular dysfunction by two-dimensional echocardiography has a high specificity and predictive value for ARVC/D [121–123]. The development of new echocardiographic techniques such as three-dimensional right ventricular (3D-RV), strain and tissue Doppler, and tissue deformation imaging, may improve the diagnostic, and prognostic performance of echocardiography in these patients, which help in minimizing the number of false-negative echocardiographic results and improve the sensitivity and specificity of this test [124]. Cardiac MRI has a significant role in the diagnosis of ARVC/D. It has the advantage of assessing the RV (and LV) function, size, global or regional wall motion abnormalities, and quantification of myocardial wall thinning and hypertrophy. The disadvantages of this technique are the lack of wide availability, and the need for interpretation by an expert specialized radiologist to prevent misdiagnosis. Incorrect interpretation of cardiac MRI is the most common cause of over diagnosis and physicians should be reluctant to diagnose ARVC/D when structural abnormalities are present only on MRI [125] (**Figure 5**). Quantitative analysis showed that RV end-diastolic diameter and outflow tract area were significantly higher and RV ejection fractions lower in ARVC/D patients when compared to controls. Although CMRI is a potentially useful test because it can distinguish fat from muscle, the sensitivity and specificity of CMRI detection of RV intramyocardial fat in the diagnosis of ARVC/D are variable, ranging from 22 to 100% [126–130]. Identifying fat can be challenging because of the thin RV wall; therefore, it is difficult to distinguish pathologic adipose infiltration from adjacent epicardial fat and it is not included in the Task Force diagnostic criteria.



**Figure 4.** Parasternal long axis (A) and apical four-chamber (B) echocardiographic views showing RV dilatation.



**Figure 5.** (A) Axial cine SSFP (steady-state free precession) MR imaging showing significant RV dilatation and (B) black-blood-prepared HASTE (Half-Fourier Acquired Single-shot Turbo spin Echo) axial slice MRI imaging at the level of RVOT showing RVOT dilatation.

## 6.2. Tissue characterization of wall (endomyocardial biopsy)

Endomyocardial biopsies (EMBs) are infrequently diagnostic, due to the focal nature of the lesions, and the fact that subendocardial layers of the myocardium are usually not affected in an early stage of the disease [131]. Furthermore, EMB sensitivity in ARVC/D is low if samples are taken from the septum, a region uncommonly involved by the disease [132]. Diagnostic values of EMB according to the new Task Force criteria are considered major if histomorphometric analysis of endomyocardial biopsies shows 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 a fatty replacement of tissue (Task 2010). If the residual myocytes are 60–75% by morphometric analysis (or 50–65% if estimated), it is considered to be a minor criterion [129].

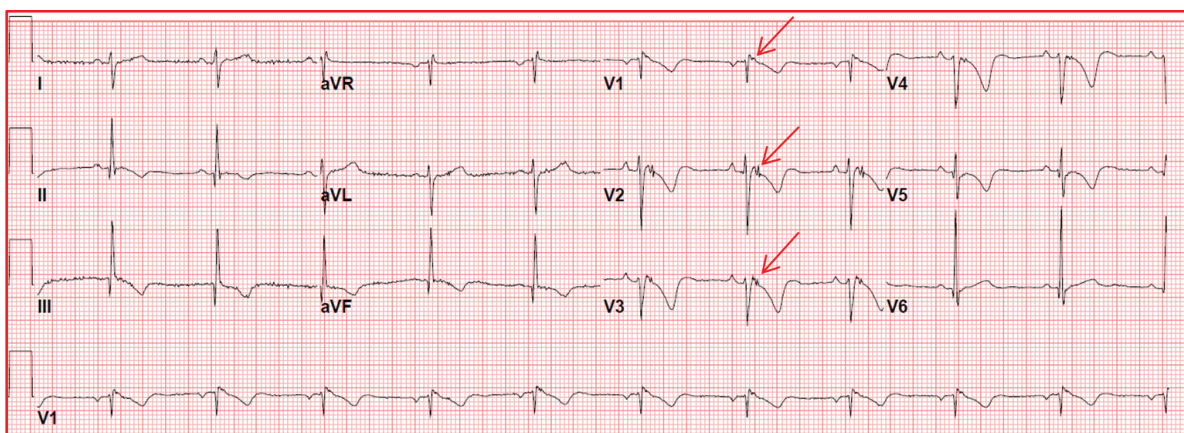
## 6.3. Electrocardiographic changes

The 12-lead ECG has a vital role in ARVC/D for diagnosis. The ECG changes and arrhythmias may precede the histological evidence of myocyte loss and RV changes in radiologic tests. Depolarization and repolarization ECG criteria have to be obtained during sinus rhythm and while off antiarrhythmic drugs.

### 6.3.1. Depolarization abnormalities

The hallmark of electrical changes in ARVC/D is the delayed RV activation. This delay may manifest with the presence of an epsilon wave, prolonged terminal activation duration (TAD) in the terminal part and after the QRS complex, and/or by recording late potentials on SAECD. Epsilon waves are defined as low amplitude potentials appearing after, and clearly separated from, the QRS complex in at least one of the precordial leads V1–V3 (**Figure 6**) [133]. Although epsilon waves are highly specific and considered to be one of the major diagnostic criteria, they are observed in only a small minority of patients [134, 135]. TAD has been defined as the longest value measured from the nadir of the S wave to the end of all depolarization deflections in V1–

V3, including the S wave upstroke and both late and fractionated signals and epsilon waves [136]. Prolonged TAD measured in V1–V3 greater than or equal to 55 ms, in the absence of complete RBBB, is considered to be a minor criterion. Prolonged TAD was recorded in 30 of 42 ARVC/D patients and only 1 of 27 patients with idiopathic VT [136]. The detection of late potentials on SAECG or late potentials detected during endocardial mapping in electrophysiologic studies (EPS) are frequently found in ARVC/D patients with documented VT; however, these late potentials can also be observed after myocardial infarction and with other structural heart diseases. Owing to this lack of specificity, SAECG abnormalities are considered a minor criterion. Common to all depolarization criteria is their correlation with disease severity. For instance, a positive correlation has been found between late potentials and the extent of RV fibrosis, reduced RV systolic function and significant morphological abnormalities on imaging [137–139].



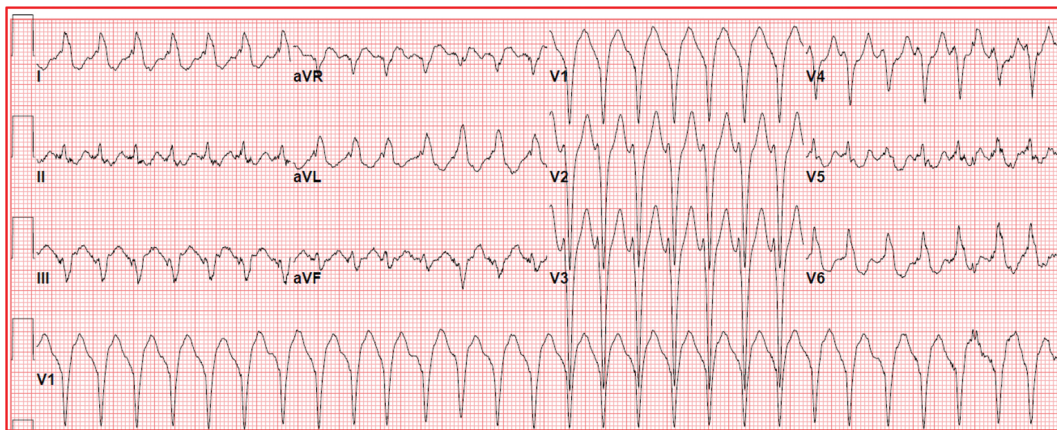
**Figure 6.** ECG of a patient with ARVC/D showing the presence of T-wave inversion in V1–V5 and an epsilon wave (electric potentials after the end of the QRS complex) (arrows).

### 6.3.2. Repolarization abnormalities

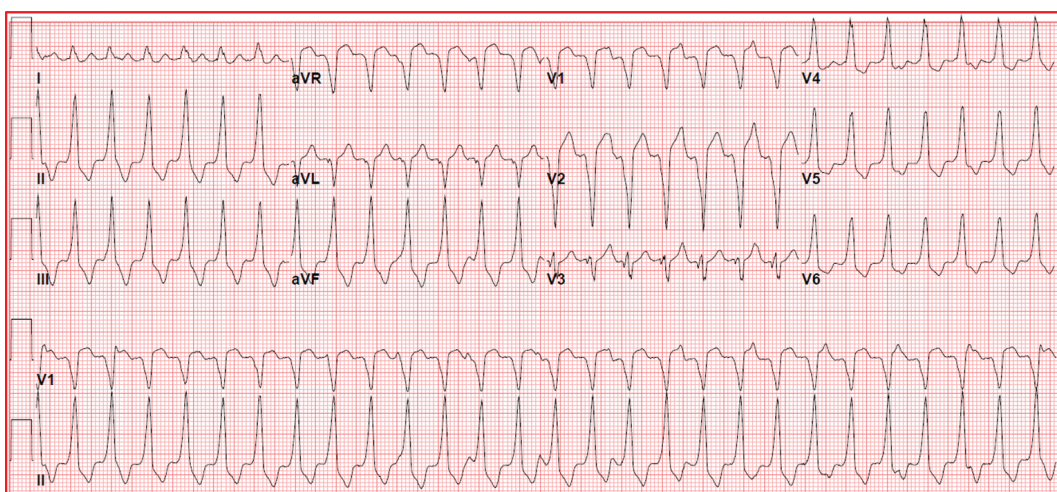
In the new Task Force criteria, negative T-waves in leads V1–V3 form a major ECG criterion in the absence of complete RBBB, but only if the patient is older than 14 years of age (**Figure 6**). T-wave inversion can be a normal feature of the ECG in children and early adolescence. Studies have reported variable prevalence of right precordial T-wave inversion, ranging from 19 to 94% [118–134, 140]. This variation may be due inclusion of family members in some studies and only index cases in others. In a study that considered only at ARVC/D index cases, 67% of them had this criterion but it was not found in patients with idiopathic RV-VT [136]. Other variants of T-wave inversion including T-wave inversion only in leads V1 and V2, T-wave inversion in V4–V6 among individuals older than 14 years of age in the absence of complete RBBB, and inverted T-waves in leads V1–V4 among individuals older than 14 years of age in the presence of RBBB, are considered to be minor repolarization criteria in the new Task Force criteria [119].

## 6.4. Arrhythmia

In ARVC/D, ventricular arrhythmias may range from PVCs to sustained VT or VF, leading to cardiac arrest [136, 141]. Typically, VT originating from RV has a LBBB-like morphology. Furthermore, VT with a superior axis (negative R waves in inferior leads) indicating RV inferior wall or apex origin (**Figure 7**) is considered a major criterion, while VT with inferior axis (positive R waves in inferior leads) indicating RV outflow tract (RVOT) origin is considered a minor criterion (**Figure 8**). VT with LBBB-like morphology and unknown axis is considered a minor criterion. Patients with the extensive disease often show multiple VT morphologies [136]. VT may degenerate into VF and lead to SCD especially in young and athletes individuals with ARVC/D. According to the new Task Force criteria, 500 or more PVCs in a 24-hour Holter recording are considered a minor criterion [119].



**Figure 7.** ECG showing ventricular tachycardia of RV inferior wall origin (LBBB and superior axis) in a patient with ARVC/D.



**Figure 8.** ECG showing ventricular tachycardia of RV outflow tract origin (LBBB and inferior axis) in a patient with ARVC/D.

### 6.5. Family history

ARVC/D is a familial disease. Having a first-degree family member with proven ARVC/D is considered an increased risk for other family members to be affected. ARVC/D confirmed in a first-degree relative who meets current Task Force criteria; ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative, or identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation is each considered as a major diagnostic criteria [119].

If a first-degree relative is diagnosed with ARVC/D but does not fulfill the diagnostic criteria, only a minor criterion is counted. Sudden death of a family member under the age of 35 years, presumably but not proven to be due to ARVC/D related arrhythmias, and ARVC/D confirmed pathologically or by current Task Force criteria in a second-degree relative is a minor criterion [119].

## 7. Differential diagnosis

It is crucial to differentiate ARVC/D from other diseases that primarily involve RV as the prognosis and management are very different. Differential diagnosis of ARVC/D includes:

1. **Right ventricular outflow tract VT (RVOT-VT):** RVOT-VT is a benign disorder that may cause exercise-induced left bundle branch block (LBBB) morphology VT with the inferior axis. In RVOT-VT there is no family history of ARVC/D or SCD, the ECG shows no depolarization or repolarization abnormalities and no RV structural changes can be detected. There is usually no reproducibly inducible VT by premature extrastimuli at programmed stimulation during electrophysiologic studies [142]. Idiopathic RVOT VT may be inducible by regular burst pacing and isoproterenol infusion [143]. The prognosis of RVOT-VT is usually good with very low risk of SCD. Furthermore, catheter ablation is usually curative in idiopathic RVOT-VT.
2. **Dilated cardiomyopathy:** Biventricular dilatation and congestive heart failure may mimic advanced ARVC/D with LV involvement. Characteristic ECG and cardiac MRI (CMRI) abnormalities in ARVC/D help to distinguish the two entities.
3. **Myocarditis:** Myocarditis due to viral infection or other causes may mimic ARVC/D. In general, endomyocardial biopsy is required to distinguish ARVC/D from myocarditis.
4. **Cardiac sarcoidosis:** Sarcoidosis is a disease of unknown etiology, characterized by the presence of noncaseating granulomas. It may affect mainly lungs, but other tissues such as heart, skin, eyes, reticuloendothelial system, kidneys, and central nervous system can be affected. About 5% of sarcoidosis patients may have cardiac involvement, which may manifest as conduction abnormalities, ventricular arrhythmias, valvular dysfunction or congestive heart failure. Although sarcoid patients typically have myocardial sarcoid granulomas and scarring in the LV and interventricular septum, the RV can also be affected. Patients can present with clinical features similar to those of ARVC/D including

arrhythmias, and SCD [144]. Visualization of granuloma in EMB can be a diagnostic value for cardiac sarcoidosis if granulomas are visualized [145]. Gadolinium-enhanced MRI may be beneficial by detecting located abnormalities in the septum, which is typical for sarcoidosis but seldom seen in ARVC/D. Positron emission tomography (PET) scans may show the active foci of sarcoidosis. Therapy with corticosteroids is recommended for patients diagnosed with cardiac sarcoidosis.

5. **Uhl anomaly:** This is a rare disorder characterized by the total lack of RV myocardium and results in a very thin-walled RV (parchment RV) [146]. In ARVC/D, the myocardium is not completely absent and is replaced by a variable degree of fibrosis.

## 8. Management

### 8.1. Risk stratification

The clinical objectives in ARVC/D management are prevention of SCD and death from heart failure; minimizing disease progression to RV, LV, or biventricular heart failure; improvement of quality of life by controlling palpitations, and minimizing appropriate or inappropriate implantable cardioverter defibrillator (ICD) discharges as much as possible; and improving functional capacity by optimization of heart failure management [147].

Therapeutic options consist of lifestyle changes, pharmacological treatment (beta-blockers, heart failure medications, antiarrhythmic medications), electrophysiological study (EPS) and catheter ablation, ICD implantation, and surgical intervention (e.g., RV isolation and heart transplantation).

### 8.2. Therapeutic options

#### 8.2.1. Lifestyle changes

There is an established relationship between SCD and intense exertion in young individuals with ARVC/D. Competitive sports activity has been shown to increase the risk of SCD by fivefold in adolescent and young adults with ARVC/D [148]. Early identification of affected athletes by preparticipation screening and their disqualification from competitive sports activity may be “life-saving” [149]. Also, physical exercise has been implicated as a factor promoting development and progression of the ARVC/D phenotype [147]. In the animal study, it was demonstrated that in heterozygous plakoglobin-deficient mice, endurance training accelerated the development of RV dilatation, dysfunction, and ventricular ectopy, suggesting that chronically increased ventricular load might contribute to worsening of the ARVC/D phenotype [150].

Studies have shown that repetitive exercise and endurance sports increase age-related penetrance, the risk of VT/VF, and occurrence of heart failure in ARVC/D desmosomal-gene carriers [151, 152]. So, patients with a definite diagnosis of ARVC/D are encouraged not participate in endurance and/or competitive sports.

### 8.2.2. *Pharmacological therapy*

#### 8.2.2.1. *Beta-blockers*

VTs and cardiac arrest in ARVC/D are frequently triggered by adrenergic stimulation and occur during or immediately after physical exercise [153–157]. Autonomic dysfunction with increased sympathetic stimulation of ventricular myocardium and subsequent reduction of  $\beta$ -adrenoceptor density were demonstrated with the use of radionuclide imaging and quantitative positron emission tomography [158, 159]. Beta-blockers are useful in the treatment of heart failure, preventing the effort-related VT, and possibly minimizing disease progression by lowering RV wall stress.

Beta-blocker therapy is recommended in ARVC/D patients with recurrent VT, as an adjunct to ICD therapy. It may also be a helpful addition to minimize inappropriate ICD shocks due to sinus tachycardia, supraventricular tachycardia, or atrial fibrillation/flutter with high-ventricular rate [147].

#### 8.2.2.2. *Heart failure therapy*

For ARVC/D patients who developed right- and/or left-sided heart failure standard pharmacological treatment with angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers,  $\beta$ -blockers, and diuretics are recommended [147].

ARVC/D patients with severe RV dilatation are at risk of thromboembolism. A 0.5% annual incidence rate of thromboembolic complications is reported during a mean follow-up period of  $99 \pm 64$  months in a cohort of 126 ARVC/D patients [160]. Long-term oral anticoagulation is indicated for secondary prevention in patients with documented intra-cavitary thrombosis or venous/systemic thromboembolism [147].

#### 8.2.2.3. *Antiarrhythmic drugs*

The aim of antiarrhythmic drug (AAD) therapy in patients with ARVC/D is to improve the quality of life by preventing symptomatic VT and ICD shocks. The data about AAD in ARVC/D are limited due to the lack of randomized control studies, the change in medication regimes over time and the common need for other modalities of treatment like VT ablation or ICD implantation [147, 161–163].

Although initial studies suggest that sotalol, administered at a dosage of 320–640 mg/day, is the most effective therapy with approximately 68% of patients achieving complete or partial arrhythmia suppression [164, 165], more recent available data suggest that amiodarone (loading dose of 400–600 mg daily for 3 weeks and then maintenance dose of 200–400 mg daily), alone or in combination with  $\beta$ -blockers, is the most effective drug for preventing symptomatic VTs and has relatively low proarrhythmic risk even in patients with ventricular dysfunction, although its ability to prevent SCD is unproven [166]. This variation in drugs effect may be partially a result of significant differences in design of the two studies, and the difference in sotalol doses, the difference in the amiodarone loading strategies and the method of medication

selection [161]. There is relatively limited data about the combination of antiarrhythmic therapy. One recent report demonstrated the effective addition of flecainide to patients receiving sotalol with a resultant reduction in recurrent arrhythmias [167]. The addition of flecainide in this study was accomplished without significant adverse events. Several other studies have reported that the combination of amiodarone and beta-blockers may be effective in patients unable to achieve arrhythmia suppression with amiodarone alone [168, 169].

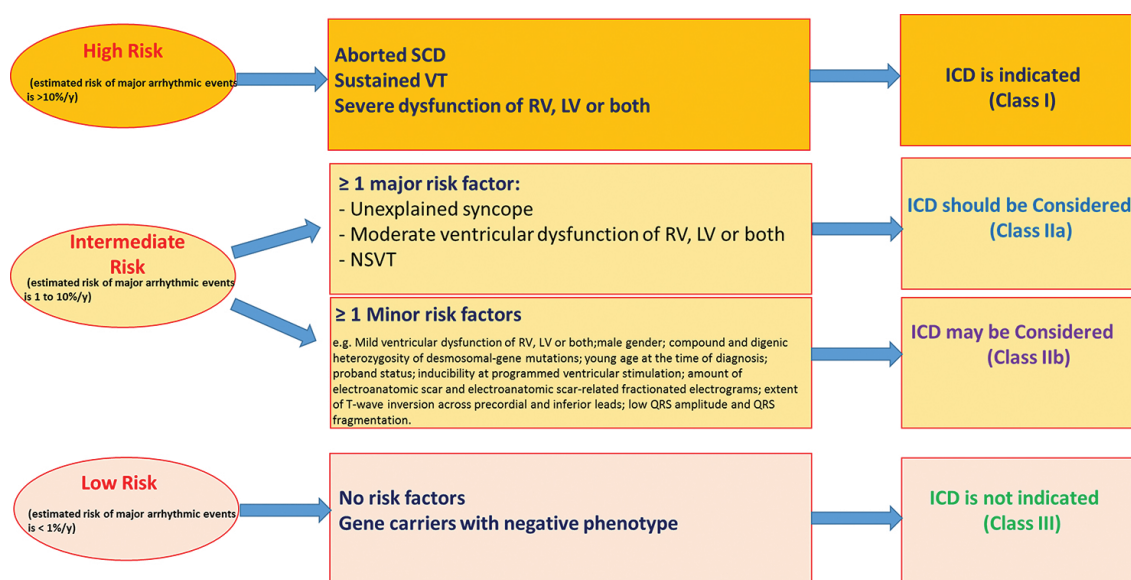
### 8.2.3. Catheter ablation

Fibrofatty replacement of RV myocardium creates scar regions that form a substrate for re-entry arrhythmias and VT.

Although VT catheter ablation is effective in the short term, the recurrence rate of VT after endocardial ablation procedures is about 50–75% in 3-year follow-up, which is likely secondary to the progressive nature of the disease [148, 170]. The discovery of the epicardial arrhythmogenic substrate in RVC/D patients makes epicardial VT ablation an attractive approach. The combination of endocardial and epicardial ablation approaches resulted in a higher success rate (77–83%) and lower recurrence of VTs over 18 and 36 month follow-up periods [171, 172]. However, this is at the expense of potential complications such as epicardial bleeding and coronary stenosis occurring in approximately 5% of cases [172]. Nevertheless, catheter ablation remains an important therapeutic modality for decreasing patient morbidity in conjunction with ICD implantation and antiarrhythmic medication especially in ARVC/D patients with incessant VT or frequent appropriate ICD interventions on VT despite maximal pharmacological therapy, including amiodarone [147, 161].

### 8.2.4. Implantable cardioverter defibrillator therapy

High-risk markers for mortality in ARVC/D include the history of syncope, sustained VT, severe RV dysfunction, and LV involvement [173–175]. ICD is the only treatment option that has been shown to reduce mortality. Over a 4-year follow-up period, the survival benefit of ICD implantation was about 25% in one study [176]. In a recent meta-analysis, the estimated annual mortality rate of patients with ARVC/D, who underwent ICD implantation, was 0.9%, significantly lower than those without ICDs [177]. A similar finding was noted in a large cohort of ARVC/D patients and family members where SCD during follow-up occurred more frequently among index-patients without an ICD (16% vs. 0.6%) [178]. The American College of Cardiology, American Heart Association and the European Society of Cardiology recommend ICD implantation for ARVC/D patients with high-risk features [179]. ICD Implantation is recommended in ARVC/D patients who have experienced hemodynamically unstable VT, sustained VT or VF (class I). Also, ICD implantation is recommended in ARVC/D patients with severe RV systolic dysfunction, LV systolic dysfunction or both (Class I). ICD implantation should be considered in ARVC/D patients who have experienced hemodynamically stable, sustained VT or who have “major” risk factors such as unexplained syncope, moderate ventricular dysfunction, or NSVT (Class IIa) [147] (**Figure 9**).



**Figure 9.** Indications for ICD in ARVC/D patients based on risk stratification. Modified with permission from Corrado et al. [147].

## 8.2.5. Surgical interventions

### 8.2.5.1. Heart transplantation

Heart transplantation is recommended as a final therapeutic option in ARVC/D patients with either severe, unresponsive congestive heart failure or recurrent episodes of VT/VF, which are refractory to catheter (and surgical) ablation and/or ICD therapy in experienced centers [147].

The most common indication for heart transplantation in ARVC/D patients is the progression of heart failure followed by intractable VTs [180]. Survival rates after 1-year post-heart transplant after were 94% and at an average follow-up of  $6.2 \pm 4.8$  year it was 88%. In a recent study involving a large cohort of ARVC/D patients, the need for cardiac transplantation was 4% [178].

### 8.2.5.2. Other surgical therapies

There is currently no clinical role for surgical therapies such as beating heart cryoablation [181], RV disarticulation [182], RV cardiomyoplasty [183], and left cardiac sympathetic denervation [184] in the treatment of patients with ARVC/D.

## 9. Family screening

ARVC/D is a familial disease and screening the family of affected individuals is important. All first-degree family members of the affected individual should be screened for ARVC/D. Screening should begin during the teenage years unless otherwise indicated. Screening tests

include ECG, signal-averaged ECG, Holter monitoring, echocardiogram, exercise stress test, and cardiac MRI. If a pathogenic mutation is identified in an ARVC/D patient, parents, siblings, and children of this patient can be tested for the mutation via the cascade method. In a recent study that looked at this matter it was found that one-third of family members fulfill conventional diagnostic Task Force criteria. Siblings are at the highest risk of disease even after correcting for age and sex, and an accurate prediction of ARVC/D diagnosis among relatives can be obtained using a model including symptoms, being a sibling, the presence of a pathogenic mutation, and female gender [185]. Meeting Task Force criteria independent of family history had a higher prognostic value for arrhythmic events than conventional Task Force criteria, which include family history. It was also noted that arrhythmic risk prediction is improved by applying modified Task Force criteria that exclude family history. This provides the physician with a reliable risk stratification tool, which does not require a difficult management scheme or additional testing [185].

## 10. Conclusions

ARVC/D is a rare cardiac disease characterized by fibrofatty replacement of myocardial tissue. It affects the RV primarily, but an extension to the LV in more advanced stages of the disease may occur. At the molecular level, both ventricles are affected, presumably in all stages of the disease. Its prevalence has been estimated to vary from 1:2000 to 1:5000. Patients typically present between the second and the fourth decade of life with VT episodes originating from the RV. It is also a major cause of SCD in the young patients and athletes.

The ARVC/D is an inherited cardiomyopathy and the causative genes encode proteins of mechanical cell junctions (e.g., plakoglobin, plakophilin-2, desmoglein-2, desmocollin-2, and desmoplakin) accounting for intercalated disk remodeling. The mode of inheritance is mostly an autosomal dominant trait with variable penetrance. The rare recessively inherited variants are often associated with palmoplantar keratoderma and wooly hair. The diagnosis is made according to the modified Task Force criteria, based on functional and structural alterations of the RV, depolarization and repolarization abnormalities, fibrofatty replacement in the endomyocardial biopsy, VT with LBBB morphology, and family history. The use of the Task Force criteria helps to avoid under an overdiagnosis of the disease. Echocardiography and cardiac magnetic resonance imaging (MRI) are the main imaging tools to visualize structural and functional abnormalities. The ARVC/D should be differentiated from other cardiac diseases such as idiopathic RVOT-VT and myocarditis. ARVC/D therapy consists of lifestyle changes, antiarrhythmic drugs, and catheter ablation. Young age at diagnosis, family history of juvenile SCD, LV involvement, VT, syncope, and previous cardiac arrest are the major risk factors for adverse prognosis. Implantable cardioverter defibrillator (ICD) therapy has been demonstrated to affect positively patients' mortality, and it should be considered in all high-risk patients. Heart transplantation may be required in about 4% of the ARVC/D patients. Ongoing research is focused on the understanding of disease pathophysiology and providing a curative therapy that may be able to stop disease progression.

## Acknowledgements

The author would like to express his appreciation to Ms. Sandra Keating and Mrs. Suzanne Tobias for editing the manuscript of this book chapter.

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