

# Arrhythmogenic right ventricular cardiomyopathy: an overview and update

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## Abstract

Arrhythmogenic right ventricular cardiomyopathy consists in partial or total progressive replacement of cardiac muscle fibers with a fibro-adipose tissue. This is a hereditary disease with an autosomal dominant inheritance with incomplete penetrance and variable expressivity, except two autosomal recessive syndromes. The most frequent abnormal proteins are that of desmosomal intercellular junctions, such as junctional plakoglobin, plakophilin-2, desmoplakin, desmoglein-2, and desmocollin-2, although other types of non-desmosomal components may be also involved. Desmosomal disorders result in myocardial fibers necrosis and their progressive replacement with fibro-adipose tissue. The morphological modifications are usually beginning in the subepicardial layer and develop towards the endocardium, being associated with the ventricular wall degeneration, thinning, and progressive increase of the amount of adipose tissue. The average age of clinical manifestations onset is around 30-40 years old, with ventricular arrhythmia and high risk of sudden death. Currently, the diagnosis is based on the 2010 Task Force Diagnostic criteria. The current review presents an overview on traditional knowledge about this disease, adding updated information regarding molecular and genetic data. The knowledge of this disease is important for medical practice as a possible cause of arrhythmia and sudden death and its prognosis might be improved by appropriate genetic testing as family screening.

**Keywords:** *ventricular arrhythmias, cardiomyopathy, dysplasia*

## Introduction

Arrhythmogenic right ventricular cardiomyopathy is a rare primary myocardial disease that is clinically characterized by life-threatening ventricular arrhythmias secondary to fibrofatty replacement of the right ventricular myocardium.

Although genetic factor plays a major role in disease determinism, the modifications are not manifested at birth.

The term "arrhythmogenic right ventricular

cardiomyopathy" (ARVC) is mostly agreed, replacing the previous name of "arrhythmogenic right ventricular dysplasia" (ARVD), still in use. A special mention should be made regarding the possibility of process extension from the right ventricle to the interventricular septum or even to the left ventricle [1].

The current term of "arrhythmogenic right ventricular cardiomyopathy" is more appropriate than ARVD, considering that the disease is not manifested at birth but its onset is later, during adult life.

## History

In 1905, Osler described a particular lesion characterized by thin ventricles ("parchmentlike"), as a necroptic finding in a young man, apparently healthy, deceased

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following a medium intensity physical activity [2].

In 1952, similar gross finding of the right ventricle was observed in a congenital disease named Uhl's anomaly [3].

In 1977, the term "arrhythmogenic right ventricular dysplasia" was introduced, being based on an abnormal development of the ventricular wall, similar to that seen in Uhl's anomaly [4, 5].

In 1986, Protonotarios Nikos, a cardiologist, reported a familial cardiac disease associated with a cutaneous syndrome [6], being named according to the Greek island of origin (Naxos disease) and later on another syndrome has been described, as Carvajal syndrome [7], both having a recessive transmission in descendants.

The term of "dysplasia" has been replaced by the designation of "cardiomyopathy" and the main diagnosis features have been set [8], as the task force criteria, with later modifications [9].

### **Brief update on myocardial fibers desmosomes**

The myocardial cells are disposed in columns, being kept together by specialized junctions, named intercalated discs. These junctions comprise cell-to-cell adhesion junctions composed of fascia adherens, gap junctions, and maculae adherentes (desmosomes). Desmosomes reinforce the fascia adherens and are parts of both transverse and lateral components of the intercalated discs [10].

The desmosomes mediate direct cell-to-cell contact by providing anchoring sites for intermediate filaments, being necessary for electrical conduction, mechanical contraction [11], participating also in tissue morphogenesis and differentiation [12]. In the area of the macula adherens, desmogleins and desmocollins provide the linkage between the plasma membranes of adjacent cells.

Electron microscopy reveals on the cytoplasmic side of the plasma membrane of each of the adjoining cells a disc-shaped structure consisting of very dense material called the desmosomal attachment plaque.

This structure measures about 400 nm x 250 nm x 10 nm and anchors intermediate filaments [13]. The filaments appear to loop through the attachment plaques and extend back out into the cytoplasm. They are thought to play a role in dissipating physical forces throughout the cell, by their attachment to the intermediate filaments. In myocardial fibers, each attachment plaque is composed of five constitutive proteins, junctional plakoglobin, plakophilin-2, desmoplakin, desmoglein-2, and desmocollin-2. Their encoding genes have been identified (Table 1) [11].

The intercellular space of the macula adherens is up to 30 nm and is occupied by a dense medial band, the intermediate line. This line represents extracellular portions of the transmembrane glycoproteins, the desmogleins and desmocollins, which are members of the cadherin family of  $Ca^{2+}$ -dependent cell adhesion molecules. In the presence of  $Ca^{2+}$ , extracellular portions of desmogleins and desmocollins bind adjacent identical molecules of neighboring cells (homotypic binding), forming a "cadherin zipper", identified in X-ray crystallographic studies. The cytoplasmic portions of desmogleins and desmocollins are integral components of the desmosomal attachment plaque. They interact with plakoglobin, desmoplakin, and plakophilin that are involved in desmosome assembly and the anchoring of intermediate filaments of desmin [10].

### **Etiology and epidemiology**

ARVC consists in partial or total progressive replacement of cardiac muscle fibers with a fibro-adipose tissue, beginning from the epicardial surface towards the endocardium. In the advanced stages of the disease, the right ventricular wall becomes extremely thin, with endocardium-epicardium apposition [12].

ARVC prevalence in general population is variable, with ranges from 1: 2 000 to 1: 5 000, with a special mention that some of these values may be even larger [13]. ARVC represents 2-5% of cases of young people sudden death, in Europe [14, 15].

According to the results of a retrospective study performed on 200 persons with sudden

death, the cause has been microscopically detected as ARVC, in 10.4% of cases [16].

As confirmed by our experience [17], males are more frequently affected compared to females, the rate between men: women being approximately 3:1 [18]. The disease is usually manifested in the second-fifth decades of life, as palpitations, syncope, and sudden death [19]. The symptoms are extremely rare under 12 years old or more than 60 years old age [20], and cardiac failure is extremely rare, manifested during late progression of the disease. An exemplifying result has been provided by a study performed on 439 patients, 36± 14 years old age, revealing a specific symptomatology in 419 patients (95%), only 20 of them being asymptomatic [21].

### Genetic syndromes and pathogeny

Genetic mutations have been identified in approximately 60% of patients [20]. The majority of cases have AD (autosomal dominant) transmission, with variable penetrance, although a minority of cases represents a manifestation of cardiocutaneous syndrome with AR (autosomal recessive) transmission, such as Naxos or Carvajal syndromes [22].

Naxos syndrome is correlated with a homozygous deletion of two base pairs found in the plakoglobin gene located in the 17q21.2 locus (Table 1) [11, 23].

ARVC in Carvajal syndrome is associated with woolly hair and palmoplantar keratoderma, as a consequence of homozygous DSP mutations in the desmoplakin gene located in the 6p24.3 locus (Table 1) [11, 24].

Although the literature considers ARVC as a genetic disease involving intercellular junctions of desmosomal-type [19, 25], there are other causative genes.

Currently, 16 mutations have been described in ARVC (Table 1), six of them being associated with desmosomal-type junctional complexes from the intercalated disks [11, 26, 27]. Relatively recent studies

have revealed that approximately 50-60% of patients with ARVC have a mutated gene encoding a desmosomal protein [28-30]. Occasionally, multiple mutations have been identified in the same patient [31].

Other types of mutations characteristic for ARVC are seen in atypical types of disease, involving non-desmosomal proteins, such as desmin (DES), transmembrane protein 43 (TMEM43), lamin-A/C (LMNA), titin (TTN), phospholamban (PLN), and  $\alpha$ -T-catenin (CTNNA3) [11, 20, 32].

A rare type of disease has been identified in 1994, involving only several families, named ARVC type 1, determined by transforming growth factor  $\beta$ -3 (TGF $\beta$ 3) mutations [33, 34], manifested as myocardial fibrosis, as a result of increased TGF $\beta$ 3 expression [11].

The pathogenic mechanism is not completely elucidated but two theories are currently under debate, namely the degeneration-inflammation model and the transdifferentiation model [1], as possible pathways of structural alterations of the right ventricular wall in ARVC.

According to the degeneration-inflammation model of pathogenesis, the alteration of myocardial intercellular adhesion results in a diminished stress resistance of cardiac muscle fibers and the most susceptible fibers are those located in the right ventricle. The necrosis and inflammation are followed by fibrosis and infiltration with adipose tissue, as a non-specific local response, analogous to the process taking place in other myocardial diseases [35].

The local inflammation, mainly expressed by accumulation of neutrophils and lymphocytes, has been described by Basso, in 1996, and has been also identified by other researchers, especially in severe types of ARVC [36, 37].

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**Table 1.** Genetic syndromes manifested by ARVC

Genotype	Genetic syndrome or other diseases	Genetic mutation	Location	Mutated proteins	Transmission type	Mutated proteins location or function
ARVC12	Naxos	JUP	17q21.2	plakoglobin	AR	Desmosome
ARVC8	Carvajal (DCM with wooly hair and keratoderma)	DSP	6p24.3	desmoplakin	AR	Desmosome
ARVC1	-	TGFB3	14q24.3	transforming growth factor $\beta$ -3	AD	Myocardial fibrosis
ARVC2	DCM CPVT	RYR2	1q43	cardiac ryanodine receptor	AD	Sarcoplasmic reticulum; cardiac contraction
ARVC3	-	unknown	14q12-q22	NA	AD	Desmosome
ARVC4	HCM DCM	TTN	2q32.1-q32.3	titin	AD	Passive restoring force of the sarcomere
ARVC5	EDMD RV aneurysm	TMEM43	3p25.1	transmembrane protein 43	AD	Nuclear membrane organizer
ARVC6	-	unknown	10p14-p12	NA	AD	NA
ARVC7	Myopathy Cardiomyopathy	DES	2q35	desmin	AD	Intermediate filament
ARVC9	-	PKP2	12p11	plakophilin-2	AD	Desmosome
ARVC10	-	DSG2	18q12.1	cadherin-like	AD	Desmosome
ARVC11	-	DSC2	18q12.1	transmembrane glycoproteins	AD	Desmosome
	DCM	PLN	6q22.1	phospholamban	AD	Calcium handling in myocardium contractions
Others	EDMD Premature aging syndrome DCM with sinus bradycardia and conduction disturbance	LMNA	1q22	lamin A/C	AD	Lining of the nuclear membrane; cells stabilization
	Long QT syndrome type 3 Brugada syndrome Progressive cardiac conduction disease DCM	SCN5A	3p21	cardiac sodium channel	AD	Rapid structural changes as response to myocardium electrical field
	-	CTNNA3	10q22.2	alpha-T catenin	AD	Binds to plakophilin; intercellular adhesion

Dilated cardiomyopathy (DCM); Catecholaminergic polymorphic ventricular tachycardia (CPVT); Hypertrophic cardiomyopathy (HCM); Emery-Dreifuss muscle dystrophy (EDMD), Not available (NA)

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Mononuclear infiltration occurrence in myocardium may also be the result of a viral infection, but viral myocarditis is not considered as an etiologic factor of ARVC [38]. The involvement of viral infections in ARVC pathogeny cannot be completely excluded, as they induce variable degrees of myocardial cells apoptosis, facilitated by genetic predisposition [31, 39].

As a consequence, it is still debated if the inflammation associated or not with viral infections with myocardial tropism is a direct cause or only a secondary manifestation of myocytary lesions characteristic for ARVC. Another plausible hypothesis is that local proinflammatory mediators may interfere with the integrity and desmosomal activity of the intercalated disks, considering their ability of plakoglobin redistribution or TGF $\beta$ 3 overexpression [36, 37]. In a transdifferentiation model, desmosomes are able to contribute to the mediation of some intercellular signals, *via* Wnt/  $\beta$ -catenin pathway, being negatively regulated by plakoglobin by nuclear competition with  $\beta$ -catenin [40]. This perturbation of the intercellular signals induces cardiac cells

apoptosis and their replacement with fibro-adipose tissue.

Arrhythmias are probably the result of gap junctions remodeling in intercalated disks and sodium flux downregulation, due to interrelationships between desmosomes, gap junctions, and voltage-gated sodium channels [41].

It is also plausible that the two mentioned mechanisms are intricated, as more as ARVC is currently considered a disease of the intercalated disk, as a carrefour of desmosomal and non-desmosomal close interactions [31, 41].

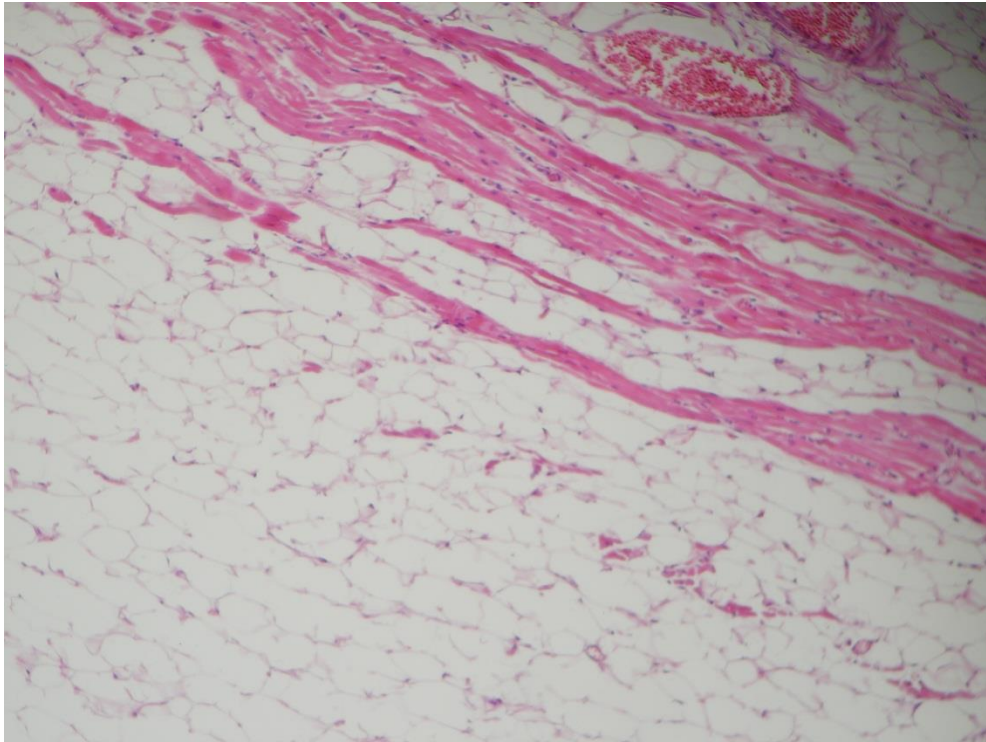
### Gross findings and histopathology

The morphologic characteristic of ARVC is the progressive replacement of right ventricle myocytes with fibro-adipose tissue (Figures 1-3). This process is initiated in subepicardial layers and progresses toward endocardium, in a different manner when compared to ischemic cardiomyopathy, resulting in ventricular wall thinning [42]. The replacement of myocardium with fibro-adipose tissue may be parcellar or diffuse [17]. In evolution, apex, infundibulum or posterior-inferior ventricular wall saccular aneurysms may occur. In late stages, the ventricular wall is extremely thin, with epicardial apposition on endocardium, termed as "papyraceous right ventricle" [26].

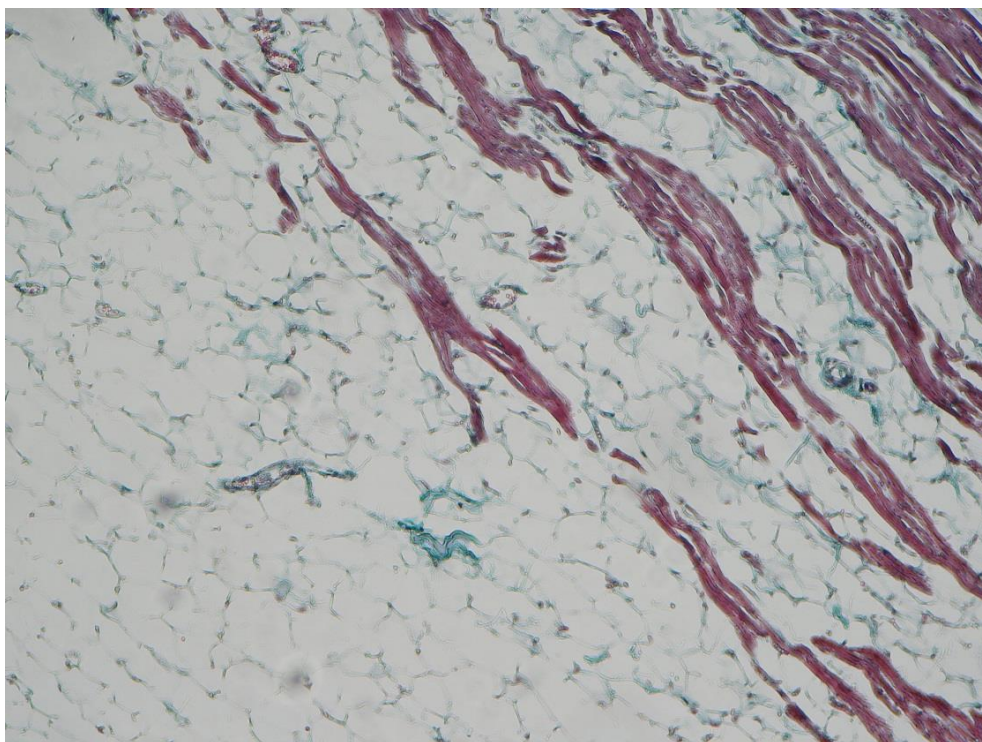
Having this classic description as a start point, necropsic studies have revealed a fibro-adipose infiltration of the left ventricle wall or, exceptionally, of the ventricular septae in patients with ARVC [1]. In rare circumstances, there are parcellar gross findings and consequently the diagnosis is only microscopical [43], as confirmed in our practical experience.

Trichromic staining may evidentiate discrete areas of fibrosis and the remodeling of intercellular intercalated disks is evident in electron microscopy [1].

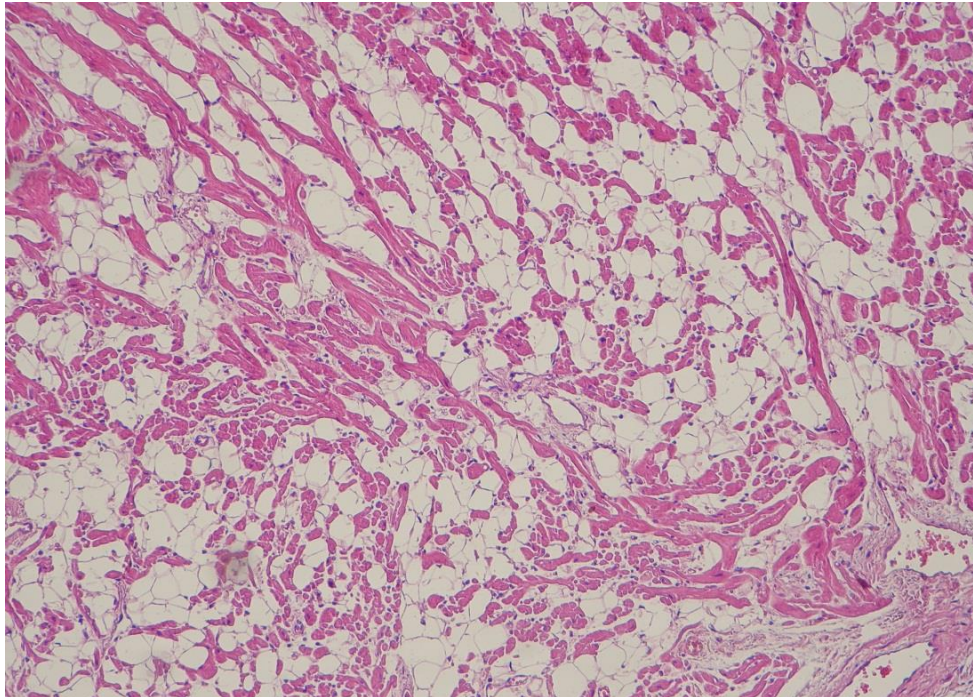
Immunohistochemical study of the desmosomal proteins is not a useful method in diagnosis as the same lesional feature may be also described in other myocardial lesions, such as sarcoidosis or giant cells myocarditis [36, 44].



**Fig. 1.** Myocardium appearance in ARVC with important decrease in cardiomyocytes number (HE, 40x)



**Fig. 2.** Myocardium appearance in ARVC with progressive fibro-adipose replacement of myocardium initiated from epicardium (Masson's trichrome, 40x)



**Fig. 3.** Fibro-adipose replacement of myocardium (HE, 40x)

### Diagnosis and differentials

A scoring system is currently used to facilitate the diagnosis, namely the Task Force Criteria (TFC), a system proposed by McKenna and co-workers, in 1994, later revised by Marcus and co-workers, in 2010 (Table 2) [43, 45].

Using this score, a specific value is attributed to family history, clinical imaging, electrocardiography, and molecular genetic testing [43]. A patient having two major criteria, or one major criterion and two minor criteria, or four minor criteria is diagnosed with ARVC. Patients having either one major criterion and one minor criterion or three minor criteria are considered as suspicious for diagnosis. The diagnosis is excluded in patients having only one major or two minor criteria [1].

The endomyocardial biopsy may be performed in cases where non-invasive paraclinical investigations are not conclusive.

However, the endomyocardial biopsies are frequently false negative, as ARVC is initiated in subepicardial areas and has a slow progression towards endocardium, so the subendocardial areas used to collect tissular

fragment may not be yet involved. Moreover, the biopsies are usually done from the interventricular septum, an area which is frequently unaffected. Not the last, the disease may be focal, and the presence of fibro-adipose tissue in myocardium is not a specific marker of the disease, as it may also occur in ischemic cardiomyopathy [1, 18].

In order to increase biopsy accuracy, the collection should be achieved from the right ventricle free wall, but this would increase the risk of cardiac tamponade.

However, myocardial endobiopsy remains the diagnosis invasive method, the general indication being to collect the fragment from the “triangle of dysplasia”, an area between the apex, infundibulum, and posteroinferior wall. The biopsies from septae or left ventricle are not useful for diagnosis [1, 20].

Nowadays, an important value in diagnosis and screening is attributed to genetic testing, though a negative result cannot exclude ARVC diagnosis [29].

A supplementary criterion to support the diagnosis is also the therapeutic response to isoproterenol, as intravenous administration of very high dose (45 mcg/min), for 3 min [46, 47]. ECG is continuously registered during the

test and 10 minutes after the administration of this drug, the test being positive if polymorphic PVCs (>3 morphologies) and if at least one couplet is observed [46, 47].

The differentials in ARVC include a multitude of heart diseases, such as: conventional dilatative cardiomyopathy, right-

sided sarcoidosis, myocarditis, and idiopathic arrhythmias. As a differential from dilatative cardiomyopathy, discordance between arrhythmias severity and ventricular dysfunction is noticed in ARVC, a feature that facilitates the differential diagnosis.

**Table 2.** The Task Force Criteria in ARVC/D – 2010

Categories	Major criteria	Minor criteria
Global or regional dysfunction and structural alterations	<p><b>By 2D echo:</b> Regional RV akinesia, dyskinesia or aneurysm</p> <p><b>By MRI:</b> Regional RV akinesia, dyskinesia or dyssynchronous RV contraction and 1 of the following:</p> <ul style="list-style-type: none"> <li>- Ratio of RV end-diastolic volume to BSA <math>\geq 110</math> mL/m<sup>2</sup> (male) or <math>\geq 100</math> mL/m<sup>2</sup> (female)</li> <li>- RV ejection fraction <math>\leq 40\%</math></li> </ul> <p><b>By RV angiography:</b> Regional RV akinesia, dyskinesia or aneurysm</p>	<p><b>By 2D echo:</b> Regional RV akinesia or dyskinesia</p> <p><b>By MRI:</b> Regional RV akinesia, dyskinesia or dyssynchronous RV contraction and 1 of the following:</p> <ul style="list-style-type: none"> <li>- Ratio of RV end-diastolic volume to BSA <math>\geq 100</math> to <math>&lt; 110</math> mL/m<sup>2</sup> (male) or <math>\geq 90</math> to <math>&lt; 100</math> mL/m<sup>2</sup> (female)</li> <li>- RV ejection fraction <math>&gt; 40\%</math> to <math>\leq 45\%</math></li> </ul>
Tissue characterization of the 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
Repolarization abnormalities	Inverted T waves in right precordial leads (V1, V2, and V3) 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 V1 and V2 in individuals $> 14$ years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 Inverted T waves in leads V1, V2, V3, and V4 in individuals $> 14$ years of age in the presence of complete right bundle-branch block
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 (V1 to V3)	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
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)
Family history	ARVC confirmed pathologically at autopsy or surgery Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation	Premature sudden death ( $< 35$ years of age) due to suspected ARVC in a first-degree relative

Right ventricle (RV), Electrocardiography (ECG), Signal-averaged electrocardiography (SAECG)



Clinical manifestations are similar in right-sided sarcoidosis, but there is characteristic involvement of the interventricular septum and atrioventricular arrhythmias, while they are rare in ARVC. Furthermore, specific granulomatous inflammation evidenced in microscopy settles the differential diagnosis.

Differential with viral myocarditis is difficult, mononuclears being evident in both microscopic specimens. Serological and genetic tests may be, in this case, useful for differential diagnosis.

### Perspectives

As the causative genes for ARVC have been identified, the premises of populational screening are met. The Sanger method represents the gold standard of sequencing, with two times of PCR applied for target exons [11]. Due to long time and high costs, next generation sequencing (NGS) methods are currently developed, being useful in whole genome, exon, or target gene sequencing [11]. With the currently available panels for genetic analysis, ARVC can be detected in a week [11].

Unfortunately, causative mutations are difficult to distinguish from other genetic noise [48]. In order to eliminate the genetic noise, data for ethnically matched controls is

necessary, associated with special softwares for prediction of pathogenic mutations to evaluate the genetic result of a patient [49]. Furthermore, the compatibility with the phenotype of the disease is needed in order to validate the genetic result [11].

### Conclusions

ARVC is a genetic disease with vital prognosis determined in a majority of cases by gene mutations. Patients have severe ventricular arrhythmias, syncope, and sudden death risk.

Light microscopy allows the observation of fibro-adipose tissue progressively replacing the right ventricular wall myocardium.

Due to the tremendous progress in elucidating the genetic determinism of ARVC, genetic testing may be used as a populational screening and premises of possible practical applications in therapy may prevent sudden cardiac death in young people.

### Conflict of interest

The authors declare that they have no competing interests.

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