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Chapter

Arrhythmogenic Right Ventricular Cardiomyopathy

Sukanya Ghosh

Abstract

Arrythmogenic right ventricular cardiomyopathy (ARVC) is a genetic form of cardiomyopathy causing fibro-fatty replacement of the myocardium. Although usually transmission is autosomal dominant, 12 genes encoding cardiac desmosomes have been found to be closely linked to this disease process shifting the congenital disease theory to a genetic one. The categorisation of ARVC as a myocyte adhesion disorder was first suggested by a molecular genetic study involving patients with Naxos disease. Misnomeric to only affect the right ventricle, ARVC also affects the left ventricle - culminating into biventricular failure as a long term prognosis. Epidemiology is well established with a male to female preponderance. It is currently the second most common cause of sudden cardiac death (SCD) in population < 35 yrs. Pathological basis of the varied clinical presentation is explained at the molecular level with myocardial atrophy, fibro-fatty replacement and chamber dilatation. Diagnosing the condition by ruling out the pitfall differentials is an enormous challenge due to the broad phenotypic spectrum including syncope on one end and SCD on the other. Task Force Criteria combines electrocardiography (ECG), echocardiography (ECHO), cardiac magnetic resonance imaging (CMRI), myocardial biopsy for diagnosis; early detection, family screening and risk stratification being the cornerstones. Therapeutic options although limited due to the progressive nature of the disease is based on preventing life threatening arrhythmias encompassing primary and secondary prevention - Implantable cardioverter -defibrillator (ICD) implantation, radiofrequency ablation and heart transplantation are the main ones.

Keywords: Arrythmogenic right ventricular cardiomyopathy (ARVC), Arrythmogenic right ventricular dysplasia (ARVD), sudden cardiac death, cardiomyopathy, genetic cardiomyopathy, cardiac desmosomes, plakophilin-2 (PKP-2), pathophysiology, diagnosis, treatment

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic form of cardiomyopathy and was initially known to primarily affect only the right ventricle (RV). It has now been found out that this disease process also may involve the left ventricle (LV) and culminate in life-threatening ventricular arrhythmias prompting sudden cardiac death (SCD) and/or biventricular heart failure [1]. ARVC is one of the leading causes of arrhythmic cardiac arrest in young people and athletes [2, 3]. The pathological hallmark of the disease is progressive loss of right ventricular myocardium and its replacement by fibrofatty tissue (**Figure 1**) [2, 4].

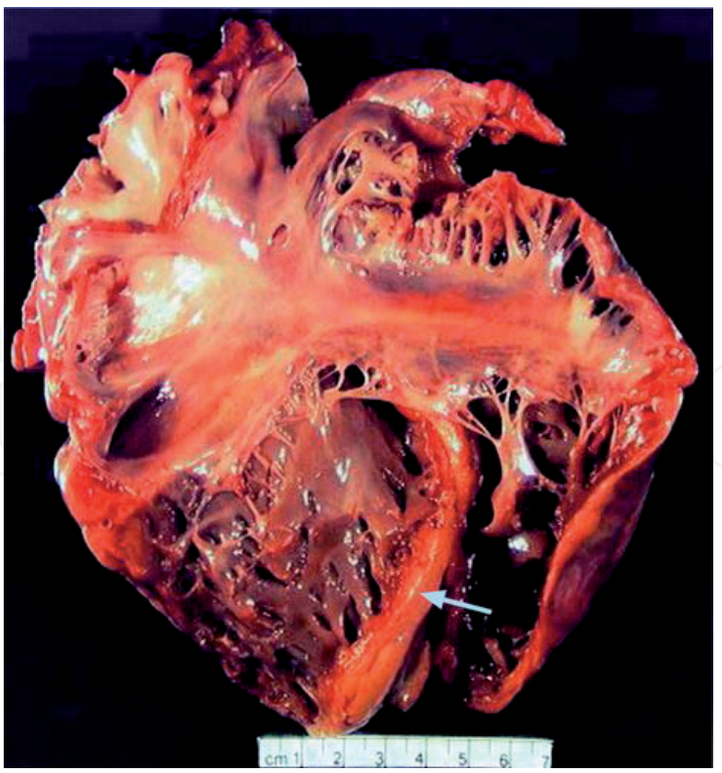

Figure 1.
Heart of a 37-year-old woman admitted with heart failure who suffered a subsequent cardiac arrest. The arrow identifies fatty infiltration of the right ventricle [9].

2. Epidemiology

The estimated prevalence of ARVC in the general population is approximately 1:5000 but in some European countries like Italy and Germany, it can be almost 1:2000, affecting men more frequently than women with a ratio of 3:1 [2] and can be explained either by a direct influence of sex hormones on the mechanisims involved in the phenotypic expression of the disease [2] or by sex based differences in the amount or intensity of exercise [2].

The exact prevalence, however, is unknown and could be higher than the estimated value because of the existence of many undiagnosed or missed diagnosed cases.

Approximately 50% of affected patients have a positive family history, but both incomplete penetrance and limited phenotypic expression are common and probably account for underestimation of the prevalence of familial disease. The disease is typically transmitted with an autosomal dominant pattern of inheritance, although rare autosomal recessive forms have been described [3].

3. History

This disease was first described in 1736 by the Pope's physician, Giovanni Maria Lancisi in his book *De Motu Cordis et Aneurysmatibus* where he mentions about a family where the affected members of the family had presented with palpitations, heart failure dilation and aneurysms of RV and SCD [4].

Dalla Volta *et al.* Reported a patient having "auricularization" the RV pressure curve, in 1961, emphasising on the peculiar haemodynamic picture of this non-ischaemic heart muscle disease where the RV was behaving like an atrium [5]. It was only in the 1980's when Drs Marcus, Nava, and Thiene found out the first clinical and pathologic series of patients with ARVC [6].

In 1982, Marcus *et al.* reported the disease in 24 adults, emphasising the origin of arrhythmias from the RV and the histopathological substrate consisting of fibrofatty replacement of the RV free wall. He also accounted for the ventricular arrhythmias of RV origin with left bundle branch block (LBBB) morphology. However, it was not until 1984 that the electrocardiographic features of ARVC were first elaborately described including the epsilon wave [6].

In 1988, Thiene *et al.* mentioned a significant series of sudden deaths in the young (< 35 years). It was noted that the pathology consisting of ARVC mostly occurred during effort and were characterised by ventricular arrhythmias of LBBB morphology and inverted T- waves in the right precordial leads in electrocardiogram (ECG). At the time this accounted for 20% of all sudden deaths in the young and this was the first time when ARVC was acknowledged as an important cause of sudden deaths in the young population [6].

ARVD1 is the first gene locus that was found by Rampazzo *et al.* in 1994 at chromosome 14q23 [5]. Basso *et al.* described the pathological profile in detail in 1996. He emphasised the frequent left ventricular (LV) involvement and the presence of an inflammatory component [6].

ARVC was included among cardiomyopathies in the revised World Health Organisation (WHO) classification in 1995 and progressive cell death (apoptosis) in myocyte was proven [6].

The need of an International Registry of the disease arose and two research programs where implemented on both sides of the Atlantic Ocean [6].

The first gene defect was discovered in the recessive variant of the disease which was originally identified in 1985 from the Naxos island and consisted of a cardiocutaneous syndrome presenting with ARVC, palmoplantar keratosis and woolly hair. A deletion was detected in the gene encoding plakoglobin which is the cell function protein [6].

Thereafter, other genes which encode cell junction proteins were found defective in the dominant, classical form of ARVC. Some of them were desmoplakin, plakophilin, desmoglein-2, desmocollin-2. These mutations accounted for intercalated disc remodelling at the ultrastructural level. The other variants of the disease were explained by mutation of ryanodine- 2 receptor and transforming growth factor beta 3 gene [6].

4. Genetics

ARVC is typically inherited as a dominant Mendelian disease, although recessive variants exist and the involvement of family members often can only be detected by directed screening. Human genetic studies in the past have offered insight into the potential causes of ARVC. Early work demonstrated substantial genetic heterogenetic T cells, and at least 9 independent loci have now been identified [7].

The genetic hypothesis has been thoroughly studied. The first chromosomal locus identified was published by Rampazzo [8] *et al.* in 1994 in Italy as previously mentioned. Linkage analysis supported the evidence for genetic heterogeneity for several ARVC loci on chromosomes (1, 2,3,6,10,12 and 14) [1, 8]. 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 type 8 [1].

In addition, the gene for Naxos disease was mapped on chromosome 17 (locus 17q21), by McCoy *et al*. [1]. This is the first disease causing gene, also named junction plakoglobin (JUP) gene (autosomal recessive variant of ARVC) [1].

The discovery of cutaneous and hair follicle involvement in recessive forms of ARVC led to the identification of mutations in the desmosomal proteins plakoglobin and desmoplakin [7]. These findings also implicated other desmosomal proteins or their partner proteins as candidate causes of the disorder. Subsequent work has revealed desmosomal mutations in a small proportion of dominantly inherited ARVC cases and in arrhythmogenic cardiomyopathy localised to the left ventricle [7]. The description of mutations in the cardiac ryanodine receptor in families with an exercise-related arrhythmia known as catecholaminergic, a polymorphic ventricular tachycardia has highlighted phenotypic distinctions from typical ARVC [7]. ARVC genetics took a significant step forward when it was discovered that mice null for the Armadillo protein plakophilin 2 (PKP 2), another desmosomal component, die at around E 11 with profound cardiac abnormalities [7]. These mice fail to form normal cardiac desmosomes, and desmoplakin disassociates from the abnormal junctions accumulating in cytoplasmic aggregates. These findings led in turn to the discovery of dominant mutations in the PKP2 gene in a large proportion of probands with ARVC and not only established mutant desmosomal proteins as a major cause of the syndrome but also raise the possibility of genetic testing as a diagnostic tool [7]. The initial report in a series of 120 and selected European probands identified PKP2 mutations in almost 1/3 of these individuals. Data from more selected cohorts of index patients with evidence of familial involvement have suggested that as many as 70% of such kindreds may have mutations in PKP2. Of note, these investigators also described evidence of founder effects for several PKP2 to mutations in remote kindreds, implying less dramatic effects on survival than are seen in other forms of ARVC [7].

A recessive mutation of DSP has been reported and associated with Carvajal syndrome, another cardiocutaneous disease [1]. PKP2 is the most frequent targeted protein with more than 25 different mutations identified in the gene encoding it. Thus, ARVC was found to be mainly a disease of the cardiomyocyte junction [2].

Furthermore, extra-desmosomal gene, unrelated to the cell adhesion complex, have been implicated as autosomal dominant forms of ARVC, such as (1). the cardiac ryanodine-2 receptor gene, responsible for the release of calcium from the sarcoplasmic reticulum; (2). the transforming growth factor beta3 gene (TGF beta3) implicated in the regulation of production of extracellular matrix and expression of genes encoding desmosomal proteins and the TMEM43 genes [1].

The cardiac ryanodine receptor gene (RyR2) has also recently been implicated in ARVC and office potential insight into the Association of Edren it adrenergically mediated ventricular arrhythmias with this disease. The ryanodine receptor induces calcium released from the sarcoplasmic reticulum into the cytosol. The cardiac ryanodine receptor has also been identified as being responsible for catecholamine-induced ventricular tachycardia. Its skeletal muscle counterpart has been implicated in malignant hyperthermia and central core disease, a congenital myopathy but the mechanisms by which mutations in the cardiac ryanodine receptor might mediate fibrofatty myocardial changes are not clear and will likely be the focus of future studies [9].

The discovery of these gene mutations allowed preliminary genotype–phenotype correlations to be made.

5. Histopathology

Characteristically, the RV in ARVC is replaced with a fibrofatty tissue. Morphologic alterations of ARVC usually begin in the subepicardium or

mediomural layers of the RV and progress to the endocardium with fibrofatty replacement of myocytes and thinning of the wall (**Figure 2**). The regions of RV most frequently involved are the RV inflow area, the apex and the infundibulum. These three areas form "the triangle of dysplasia" [9]. However, small amounts of fat are present in the epicardial layer and within the RV myocardium in normal subjects. Fontaine *et al.* examined the hearts at necropsy in 140 individuals with no history of heart disorders. Over 50% of the subjects had fat within their RV myocardial fibres, and the presence of intramyocardial fat increased with age. Therefore, histologic diagnosis of ARVC may be difficult in borderline cases. To avoid overdiagnosing ARVC, Angeline *et al.* have proposed that the presence in biopsy sections of more than 3% of fibrous tissue and more than 40% of fatty tissue is highly suggestive of ARVC. These authors also emphasised the importance of identifying coexisting myocardial fibrosis in making the diagnosis. In a forensic autopsy study of 20 patients with ARVC who died suddenly, the fatty replacement involved the outer half of the RV free wall in 27%, the other 2/3 in 28% and the entire wall thickness in 45% of the cases [9]. Interestingly, the endocardial muscular trabeculae are generally spared but may occasionally also be atrophied. The LV was involved in 40% of cases in this report, although other reports have the identified LV involvement in up to 76% of individuals with ARVC examined at necropsy. When the LV is involved, the fibrofatty replacement can affect both the septum and LV free wall, either diffusely or, more often, regionally with a predilection for the posteroseptal and posterolateral areas. In the LV, fatty replacement of the myocardium has a predilection for the subepicardial and midventricular wall [9].

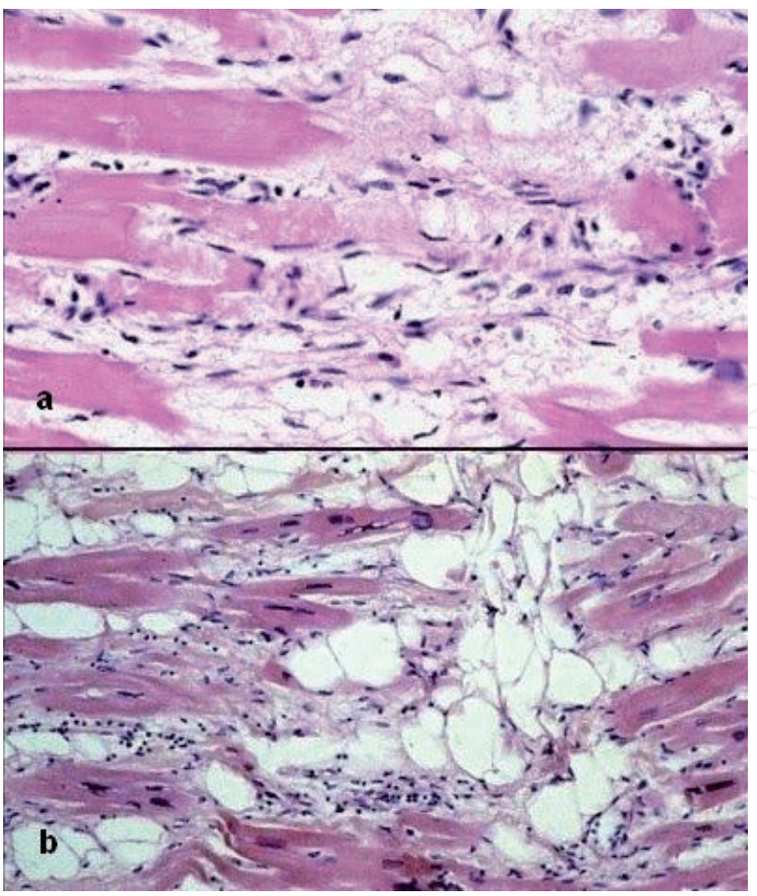

Figure 2.
Typical histologic features of ARVC/D. ongoing myocyte death (a) with early fibrosis and adipocytes infiltration (b) [6].

6. Pathogenesis

ARVC 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 [1]. 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 recognised as a desmosomal disease. In addition, myocardial atrophy is the consequence of cell death after birth and its progressive postnatal development has been definitely assessed. This concept has evolved over the last 30 years and based on its clinical characteristics, pathophysiology, postnatal development and genetic background, its inclusion in the World Health Organisation (WHO) classification of cardiomyopathies was finally achieved [1].

Several studies have been performed to determine the aetiology and pathogenesis of ARVC. However, there is still conflicting evidence. Different courses have been suggested as congenital defects, genetics and acquired factors [1]. In approximately 30–50% of cases it is transmitted with an autosomal dominant pattern of inheritance, with incomplete penetrance and variable expression [1].

Acquired factors have also been suggested as the cause of ARVC. The strongest association has been made with viral myocarditis inducing arrhythmogenic cardiomyopathy due to histopathological similarity between the two of lymphocytic infiltrate with disappearance of myocytes and fibrofatty replacement [1].

How do the mutant junctional proteins result in a unique, predominantly right ventricular cardiac phenotype? Desmosomal proteins are widely expressed, so the focal nature of apparent pathology in both dominant and recessive ARVC led to initial speculation on the role of mechanical stresses. Impaired desmosome function under conditions of mechanical stress was proposed to predispose to cardiomyocyte detachment and death, with subsequent inflammatory reaction and fibrofatty replacement. However, consideration of the distribution of skin lesions in recessive variants infers that this mechanism alone is unlikely to be responsible. Several areas of the body subject to substantial physical stresses are not involved, while the hair follicles are uniformly affected. In addition, the prominent adipose replacement suggests not scarring and healing, but rather a more fundamental perturbation of primary tissue architecture [7].

Three different types of intercellular junction are distinguished at the cardiac intercalated disc: (a) adherens junctions, which anchor actin filaments; (b) desmosomes, which anchor intermediate filaments; and (c) gap junctions, which mediate ion transfer. Cardiac myocytes rely on these specialised structures for both mechanical and electrical coupling of the myocardial syncytium [7]. Desmosomes may protect other junctions from mechanical stress, but they also have been implicated in the structural organisation of the intercalated disc. Desmosome dependent orchestration of local membrane and cytoplasmic domains may be critical for many of the physiologic functions of the intercalated disc. For example, the destabilisation of cell adhesion complexes may perturb the kinetics of gap junction turnover, resulting in heterogeneous conduction, a potential contributor to arrhythmogenesis in ARVC [7].

Desmosomes also participate in intercellular signalling networks, of which the Wnt/beta-catenin pathway is the most extensively studied. In the archetypal pathway the cytoplasmic concentration of beta-catenin is exquisitely regulated by multiple inputs, including secreted ligands of the Wnt family and recruitment of beta-catenin to intercellular junctional complexes. Cytoplasmic accumulation of beta-catenin leads to its nuclear translocation, association with the T-cell factor/lymphoid enhancer factor (Tcf/Lef) family of transcription factors and subsequent changes in gene expression. This evolutionarily conserved pathway plays a central

role in many of the most fundamental cellular behaviours and has been directly implicated in the regulation of cell fate, proliferation, and apoptosis. Importantly, the various pathway components are duplicated in higher organisms, and specific isoforms may even be employed serially for discrete functions at different times and at different sites. In addition, superimposed on the basic structure of the Wnt/beta-catenin signalling network are many subtle feedback loops and points of cross-talk that are only beginning to be uncovered [7].

Elegant immunohistochemical studies have shown that the mutant form of the plakoglobin protein fails to integrate into desmosomes and shifts from intercalated discs to site cytosol and nuclear pools, where it causes changes in nuclear signalling and the transcriptional activity, in particular through pathways regulated by the protein beta-catenin [2].

The fibrofatty tissue that replaces myocardium in ARVC is thought to contribute to the development of ventricular arrhythmias by slowing intraventricular conduction and acting as a substrate for arrhythmias through a scar related macroreentry mechanism, similar to that observed after myocardial infarction. Life-threatening ventricular arrhythmias in ARVC may also be the result of mechanisms operating at the molecular and cellular levels. Desmosomes, sodium channels, and gap junction proteins interact synergistically to regulate adhesion, excitability, and coupling of myocytes; this coordinated network of proteins located at the intercalated discs has been termed the "connexome" [2]. Loss of expression of desmosomal proteins may cause (or contribute to) potentially fatal arrhythmias by inducing gap junction remodelling, with reduction of total content and substantial redistribution of the gap-junction protein connexin 43, and decreasing the amplitude and kinetics of the sodium current [2].

The Brugada syndrome is a cardiac ion-channel disorder caused by a genetic deficiency in sodium channel function. There is some evidence that the Bruguda syndrome and ARVC may share clinical features and arrhythmic mechanisms as a result of their common origin from the connexome [2].

7. Clinical presentation

The onset occurs usually after childhood, with palpitations and/or syncope. The following clinical pictures have been observed [6]: **1. Subclinical face with concealed structural abnormalities**-the affected patient has no symptoms, and cardiac arrest may be the first and last manifestation of the disease. ARVC has been reported as one of the leading causes of sudden death in the young [6]. **2. Overt electrical disorder**-with palpitations and syncope. The most typical clinical presentation of the disease is symptomatic ventricular arrhythmias of RV origin, usually triggered by effort. Arrhythmias range from isolated premature ventricular beat to sustained ventricular tachycardia (VT) with LBBB morphology up to ventricular fibrillation leading to cardiac arrest. The QRS morphology and axis during VT reflect its site of origin. A LBBB with inferior axis suggests an origin from the RV outflow tract (RVOT), while a LBBB with superior axis suggests an origin from the RV inferior wall. However, VTs with LBBB morphology are not specific for ARVC. Basal ECG may disclose inverted T waves in the right precordial leads (a T wave inverted beyond V1 after 14 years of age is almost pathognomonic of ARVC/D) (**Figure 3**) [6]. QRS enlargement of more than 110 ms and epsilon waves are strongly indicated of intraventricular impulse conduction delay. Signal average ECG may help to disclose fragmented low amplitude late potentials at the end of the QRS complex [6].

3. Heart failure- The progressive loss of the RV myocardium may impair the mechanical function of the RV and account for severe pump failure [6].

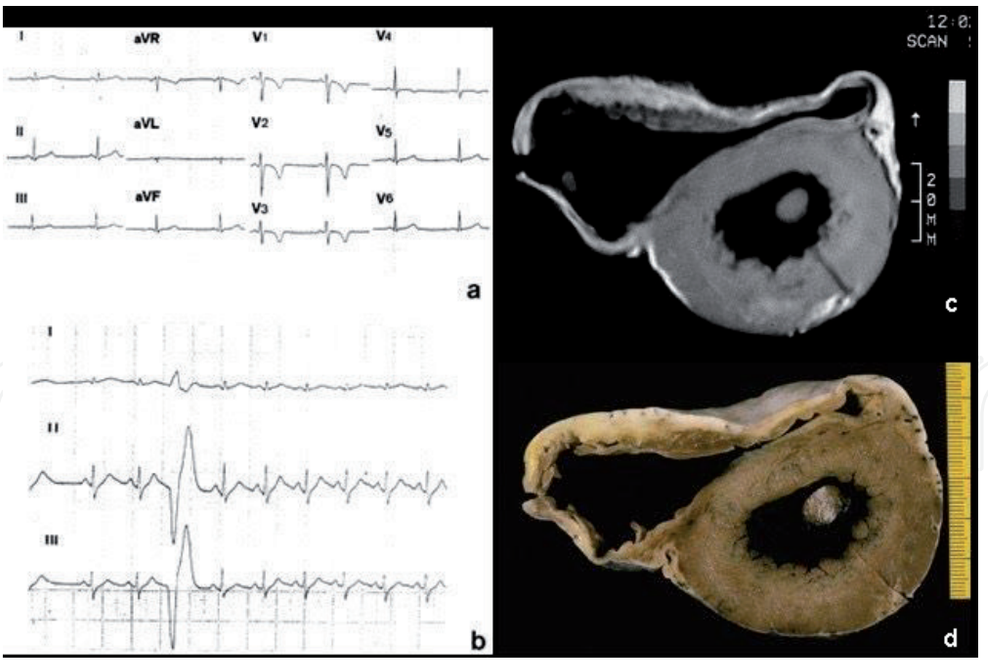

Figure 3.
A 17 year old asymptomatic male athlete who died suddenly during a soccer game. 12 lead ECG showing inverted T waves up to V4 (a) and isolated premature ventricular beats (b). In vitro MRI (c) and corresponding cross section of the heart (d) show RV dilatation with anterior and posterior aneurysms [6].

4. Biventricular failure- When the disease involves the ventricular septum and the LV, congestive heart failure occurs, mimicking dilated cardiomyopathy. Endocavitary mural thrombosis may occur, especially within aneurysms or in the atrial appendages when heart failure is complicated by atrial fibrillation, as to account for thromboembolism. In such conditions, contractile dysfunction may be so severe as to require cardiac transplantation. Clearly, when LV is affected ventricular arrhythmias may appear polymorphic, originating from different cardiac regions. The occurrence of fatal outcome, mostly sudden death varies between 0.1–3% per year in adults with diagnosed and treated ARVC, but it is unknown and may be higher in adolescents and young adults, in whom the disease is concealed and the first manifestation can be sudden death [6].

8. Diagnosis

To standardise the clinical diagnosis of ARVC, in 1994 an international task force proposed guidelines in the form of a qualitative scoring system with major and minor criteria [2]. In 2010, the task force revised the guidelines to improve diagnostic sensitivity, mostly for the clinical screening of family members, by providing quantitative criteria for diagnosing right ventricular abnormalities and adding molecular genetic criteria [1] (**Table 1**). However, the diagnosis remains problematic because of the low specificity of electrocardiographic abnormalities, multiple causes of right ventricular arrhythmias, difficulties in the use of imaging to assess right ventricular structure and function, and the sometimes puzzling results of genetic testing.

The diagnosis is particularly challenging in children, because clinical manifestations of earlier ARVC are subtle [2]. Cardiac Magnetic Resonance Imaging (MRI) is an attractive imaging toolBecause it is non-invasive and has the ability to characterise tissue by distinguishing fat from muscle [6] (**Figure 4**) and has proved to be more sensitive than electrocardiography for detecting early ventricular dilatation and dysfunction in children [2].

I. Global or regional dysfunction/structural alterations	
Major	2D TTE
	Regional RV akinesia, dyskinesia or aneurysm
	and 1 of the following criteria (end diastole):
	• PLAX RVOT ≥32 mm (PLAX/BSA] ≥19 mm/m^2)
	• PSAX RVOT ≥36 mm (PSAX/BSA] ≥21 mm/m^2)
	or RV fractional area change ≤33 %
	CMR
	Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction
	and 1 of the following criteria (end diastole):
	• RV end-diastolic volume /BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
	or RV ejection fraction ≤40 %
	RV Angiography
	Regional RV akinesia, dyskinesia or aneurysm
Minor	2D TTE
	Regional RV akinesia, or dyskinesia
	and 1 of the following criteria (end diastole):
	• PLAX RVOT ≥29–31 mm ([PLAX/BSA] ≥16–18 mm/m^2)
	• PSAX RVOT ≥32–35 mm ([PSAX/BSA] ≥18–20 mm/m^2)
	• RV fractional area change >33–39 %
	CMR
	Regional RV akinesia, dyskinesia or dyssynchronous RV contraction
	and 1 of the following criteria (end diastolic):
	• RV end-diastolic volume/BSA ≥100–109 mL/'m^2 (male) or ≥90–99 mL/m^2 (female)
	or RV ejection fraction >40–44 %
II. Histopathology (endomyocardial biopsy)	
Major	Residual myocytes <60 % by morphometric analysis (or <50 % if estimated), with fibrous replacement of the RV free wall myocardium
	≥1 sample, with or without fatty replacement
Minor	Residual myocytes 60–75 % by morphometric analysis (or 50–65 % if estimated), with fibrous replacement of the RV free wall
	≥1 sample, with or without fatty replacement
III. Repolarisation abnormalities (14 years of age)	
Major	T-wave inversions V1–3 or beyond (in absence of complete RBBB)
Minor	T-wave inversions V1–2 or V4–6 (in absence of complete RBBB)
	T-wave inversions VI–4, if complete RBBB present
IV. Depolarisation abnormalities	

Major	ε wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in V1–3
Minor	Signal-averaged ECG with late potentials (if QRS on standard surface ECG <110 ms)
V. Arrhythmias	
Major	Non-sustained or sustained ventricular tachycardia (VT) of LBBB morphology with superior axis
Minor	Non-sustained or sustained VT of RVOT configuration, LBBB morphology with inferior axis or of unknown axis
	>500 VES per 24 h (Holter)
VI. Family history	
Major	ARVC/D 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 categorised as associated with ARVC/D in index patient
Minor	Suspected ARVC/D in a first-degree relative (current Task Force criteria can not be determined)
	Premature SCD (<35 years of age) due to suspected ARVC/D in a first-degree relative
	ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relatives

Definite diagnosis: two major or one major and two minor criteria or four minor from different categories; Borderline diagnosis: one major and one minor or three minor criteria from different categories; Possible diagnosis: one major or two minor criteria from different categories BSA - body surface area; CMR - cardiac magnetic resonance tomography; ECG - electrocardiogram; LV - left ventricle; PLAX - parasternal long-axis view; PSAX - parasternal short-axis view; RBBB - right bundle branch block; RVOT - RV outflow tract; RV - right ventricle; TTE - transthoracic echocardiogram; VES - ventricular extrasystole; VT - ventricular tachycardia.[102]

Table 1.
Revised 2010 task force criteria for diagnosis of ARVC/D [1].

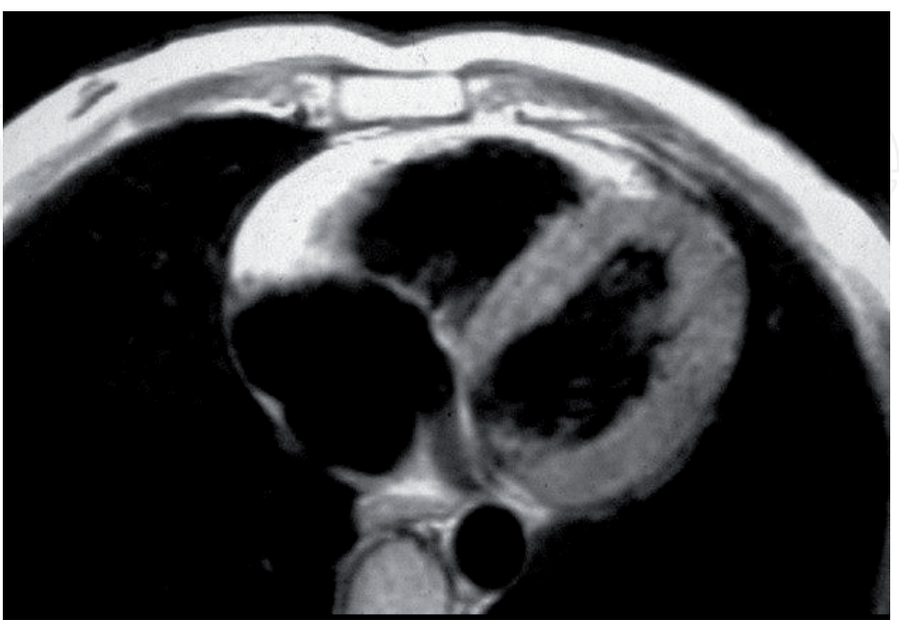

Figure 4.
MRI in a patient affected by ARVC/D (long axis view of the right ventricle): Note the transmural diffuse bright signal in the RV free wall on spin echo T1 (a) due to massive myocardial atrophy with fatty replacement (b) [6].

Conditions that may be difficult to differentiate from ARVC include idiopathic right ventricular outflow-tract tachycardia, cardiac sarcoidosis, and continental heart disease leading to right ventricular volume overload. Biventricular variants of the disease with severe left ventricular involvement may be indistinguishable from dilated cardiomyopathy. The difficult differential diagnosis, together with referral bias, may account for the discrepancies in the reported incidence of heart failure in patients with ARVC [2].

9. Risk stratification

The clinical course of ARVC is characterised by the occurrence of arrhythmic events, which can cause SCD, and the impairment of biventricular systolic function, which can lead to death from heart failure. The estimated overall mortality varies among studies, ranging from 0.08–3.6% per year [2]. The mortality was initially overestimated because it was based on studies at tertiary referral centres which predominantly included high-risk patients. Recent studies of community-based patient cohorts have shown that the long-term outcome for treated index patients and family members is favourable- annual mortality <1% [2].

The prognosis for patients with ARVC depends largely on the severity of arrhythmias and ventricular dysfunction. Prior cardiac arrest due to ventricular fibrillation and sustained VT are the most important predictors of life-threatening arrhythmic events during follow-up. Major risk factors include unexplained syncope, non-sustained VT on ambulatory monitoring or exercise testing, and severe systolic dysfunction of the RV, LV or both.

Although intracardiac electrophysiological testing has traditionally been used to assess the risk of ventricular arrhythmias, the prognostic value of VT or ventricular fibrillation induced by programmed ventricular stimulation in patients with asymptomatic ARVC remains unclear [2].

10. Management

The aims of clinical management of ARVC are to reduce the risk of sudden cardiac death and improve the quality of life by alleviating arrhythmic and heart failure symptoms. Restriction from intense sports activity (physical exercise may aggravate mechanical uncoupling of myocytes) is regarded as an important preventive tool for both healthy gene carriers and clinically affected persons in order to protect them from the risk of exercise-related malignant arrhythmic events and disease development or progression. The available evidence indicates that family members with a negative phenotype (either healthy gene carriers or those with an unknown genotype) do not need any specific treatment other than sports restriction; however, lifelong clinical assessment with the use of non-invasive tests at least every 2 years is warranted because of the age-related penetrance and progressive nature of ARVC [2].

Despite limited supportive data, beta-blockers are currently recommended for all clinically affected persons, for both prevention of arrhythmias and reduction of right ventricular wall stress. In patients with ventricular arrhythmias, antiarrhythmic drugs therapy offers the potential to ameliorate symptoms, although there is no proof that it confers protection against sudden cardiac death. Amiodarone, alone or in association with beta-blockers, and sotalol are the most effective drugs, combining the synergistic effects of class III antiarrhythmic properties and beta adrenergic

blockade. The potential for serious cumulative toxic effects precludes long-term therapy with amiodarone, especially in younger patients [2].

Catheter ablation is a therapeutic option for patients who have episodes of sustained, monomorphic ventricular tachycardia. However, it should be regarded as a palliative rather than curative therapeutic approach because of the high frequency of subsequent recurrences of ventricular tachycardia and the unproven efficacy of ablation as a means of preventing sudden cardiac death. The poor long-term outcome has been attributed to the progressive nature of ARVC, which leads to the development of multiple arrhythmogenic foci over time. The epicardial location of some ventricular tachycardia reentry circuits, which reflects the propensity of ARVC lesions to originate and progress from the epicardium, may also explain the failure of conventional endocardial mapping and catheter ablation. Several studies have shown the feasibility and efficacy of epicardial catheter ablation for patients in whom one or more endocardial procedures have been unsuccessful [2].

Since surgical isolation of RV free wall (a therapeutic approach previously) risks postoperative RV failure, this procedure has been replaced by Implantable cardioverter-defibrillator (ICD) placement [1]. Although randomised trials of defibrillator therapy have not been performed, data from observational studies have consistently shown that it is effective and safe. Patients who benefit most from defibrillators (ICD) are those who have had an episode of ventricular fibrillation or sustained ventricular tachycardia. It remains uncertain whether defibrillator therapy is appropriate for primary prevention of sudden cardiac death among patients with one or more risk factors and no prior major arrhythmic events [2].

In asymptomatic patients with no risk factors and in healthy gene carriers, there is generally no indication for prophylactic defibrillator implantation because of the low risk of arrhythmias and the significant risk of device and electrode-related complications during long-term follow-up [2]. It has become apparent that defibrillators may be inappropriately implanted in patients with a false diagnosis of ARVC based on misinterpretation of cardiac MRI studies [2].

Patients in whom right or left heart failure develops are treated with a standard pharmacologic therapy, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and diuretics. Therapy with oral anticoagulants is reserved for patients with atrial fibrillation or thromboembolic complications. Cardiac transplantation is the ultimate therapy for patients with untreatable arrhythmias (e.g. incessant storms of ventricular tachycardia or fibrillation) or congestive heart failure that is refractory to pharmacologic and nonpharmacologic therapies [2].

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 [1].

Current therapeutic approaches to ARVC are palliative and partially alleviate symptoms and the risk of sudden cardiac death but do not prevent the development or progression of the disease process. A definitive curative treatment will require a deeper knowledge of the biologic mechanisms and environmental factors involved in the pathogenesis of ARVC. A recent observation concerns a small molecule designated SB216763, which is an activator of the Wnt signalling pathway. This molecule has been shown to prevent or reverse phenotypic manifestations of ARVC induced by overexpression of defective plakoglobin in a zebrafish model, as well as in rat cardiac myocytes. Although this drug is of interest as a potential mechanism-based therapy of ARVC, it has not yet been studied in humans [2].

11. Conclusion

ARVC is a progressive disease with life-threatening complications, which constitute a clinical diagnostic challenge for physicians, given the different genotype and phenotypic variations and the wide ranges of clinical manifestations. The main challenges to improve the risk stratification for better identification of high risk patients of SCD and heart failure, 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 [1].

ARVC at a quick glance

- Arrythmogenic right ventricular cardiomyopathy (ARVC) is a genetic form of cardiomyopathy causing fibro-fatty replacement of the myocardium.
- Transmission is usually autosomal dominant, with a male to female preponderance.
- The desmoplakin gene (DSP), the first desmosomal protein gene to be associated with a major form of the disease.
- ARVC is a myocyte adhesion disorder.
- ARVC is currently the second most common cause of SCD in the young population.
- Pathophysiology includes myocardial atrophy, fibrofatty replacement, and chamber dilatation.
- ARVC presents a diagnostic challenge- 2010 revised task force criteria for ARVC, ECG, echocardiogram, cardiac MRI, myocardial biopsy, family screening and risk stratification being the cornerstones.
- Therapeutic options are based on preventing life-threatening arrhythmia– both primary and secondary prevention – starting from ICD and radiofrequency ablation to heart transplantation in patients with late complications.

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Abbreviations

ARVC	Arrhythmogenic right ventricular cardiomyopathy
ARVC/D	Arrhythmogenic right ventricular cardiomyopathy/dysplasia
ICD	Implantable cardioverter-defibrillator
LBBB	Left bundle branch block
LV	Left ventricle
MRI	Magnetic Resonance Imaging
PKP2	Plakophilin 2
RV	Right ventricle
RVOT	Right ventricle outflow tract
SCD	Sudden cardiac death
TGF	Transforming growth factor
VT	Ventricular tachycardia
WHO	World Health Organisation

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