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REVIEW

Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update

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Abstract Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a predominantly genetically determined and heritable form of cardiomyopathy that is characterized pathologically by the replacement of myocytes by adipose and fibrous tissue and leads to right ventricular failure, arrhythmias, and sudden cardiac death. The estimated prevalence of ARVC/D in the general population ranges from 1 in 2,000 to 1 in 5,000, men are more frequently affected than women, with an approximate ratio of 3:1. ARVC/D can be inherited as an autosomal dominant disease with reduced penetrance and variable expression, autosomal recessive inheritance is also described. There have been 12 genes identified which are linked to ARVC/D, encoding several components of the cardiac desmosome. Dysfunctional desmosomes resulting in defective cell adhesion proteins, such as plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP-2), and desmoglein-2 (DSG-2) consequently cause loss of electrical coupling between cardiac myocytes, leading to myocyte cell death, fibrofatty replacement and arrhythmias. Diagnosis is based on the finding a combination of characteristic abnormalities in family history, electrocardiography, cardiac imaging as well as endomyocardial biopsy (original task force criteria). Therapeutic options remain limited because of the progressive nature of ARVC/D. Competitive athletics should be avoided. Patients with ARVC/D with a history of having been resuscitated from sudden cardiac death, patients with syncope, very young patients, and those who have marked right ventricular involvement are at the highest risk for arrhythmic death and also, the presence of left ventricular involvement is a risk factor. Several authors concluded that patients who meet the Task Force criteria for ARVC/D are at high risk for sudden cardiac death and should undergo ICD placement for primary and secondary prevention, regardless of electrophysiologic testing results. The role of electrophysiologic study and VT catheter ablation in ARVC/D remains poorly defined, and is frequently used as a palliative measure for patients with refractory VT. The progressive nature of ARVC/D suggests that catheter ablation would not be a long-term curative procedure. Sotalol proved to be highly effective in patients with ARVC/D and inducible as well as non-inducible ventricular tachycardia; if it is ineffective in inducible ventricular tachycardia response to other antiarrhythmic drugs is unlikely and therefore non-pharmacological therapy without further drug testing should be considered. Orthotopic heart transplantation is considered in patients with progressive heart failure and intractable recurrent ventricular arrhythmias

Keywords ARVC/D · Arrhythmogenic right ventricular cardiomyopathy/dysplasia · Fibrofatty degeneration · Ventricular fibrillation · Arrhythmias · Sudden cardiac death · Diagnosis · Echocardiography · Electrocardiography · Magnetic resonance imaging · Implantable cardiac defibrillator · ICD · Ablation

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Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a predominantly genetically determined

and heritable form of cardiomyopathy that primarily affects the right ventricle and is characterized pathologically by the replacement of myocytes by adipose and fibrous tissue [1]. ARVC/D is transmural and frequently localized in the inflow tract, outflow tract, or apex of the right ventricle (RV)—the so-called "triangle of dysplasia"—and accounts for aneurysmal dilatation [2]. The estimated prevalence of ARVC/D in the general population ranges from 1 in 2,000 to 1 in 5,000 [3]. The disease affects men more frequently than women, with an approximate ratio of 3:1, and is a major cause of sudden death in the young and in athletes.

ARVC/D was initially believed to be a developmental defect of the RV myocardium, leading to the original designation of "dysplasia" [4]. Because the first anatomical and clinical description of the disease in 1977 by Fontaine et al. [5], there have been considerable achievements in our understanding of ARVC/D. Consensus diagnostic criteria were developed which included MRI, echocardiography, electrocardiography and right ventricular biopsy [6]. The right ventricular biopsy is definitive when typical fibrofatty replacement of myocardium is visible, but often gives a false-negative result because of the segmental nature of ACVC/D [7].

Clinically, ARVC/D is characterized by functional abnormalities of the right ventricle, electrocardiographic depolarization/repolarization changes, syncope, and ventricular arrhythmias which may lead to sudden death [8]. ARVC/D cannot be regarded as an isolated disease of the right ventricle; according to Corrado et al. [9] left ventricular involvement, typically of the posterior lateral wall, was found in 76% of hearts with ARVC/D. Left ventricular involvement is age-dependent and associated with clinical arrhythmic events, severe cardiomegaly, inflammatory infiltrates and heart failure.

Fatty infiltration of the right ventricle cannot be considered per se a sufficient morphologic hallmark of arrhythmogenic right ventricular cardiomyopathy; a certain amount of intramyocardial fat is present in the right ventricular anterolateral and apical regions even in the normal heart. Both, the fibrofatty and fatty variants of ARVC/D show, besides fatty replacement of the right ventricular myocardium, degenerative changes of the myocytes and interstitial fibrosis, with or without extensive replacement-type fibrosis [10].

Inheritance

ARVC/D can be inherited as an autosomal dominant disease with reduced penetrance and variable expression, although autosomal recessive forms of inheritance also occur [11, 12]. Molecular genetic analysis has provided considerable progress in understanding the pathophysiology of ARVC/D, showing that mutations in genes encoding several components of the cardiac desmosome can been associated with ARVC/D, resulting in defective cell adhesion proteins, such as plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP-2), and desmoglein-2 (DSG-2) [11–14] (Table 1). The data of Xu et al. [15] suggested that the genetic basis of ARVC/D includes reduced penetrance with compound and digenic heterozygosity.

Despite the genes coding for the desmosomal proteins, other gene mutations were found in patients with ARVC/D, involving the transforming growth factor (TGF)-β3, which encodes for a cytokine-stimulating fibrosis and modulating cell adhesion [16, 17], the human ryanodine receptor 2 which induces the release of calcium from the myocardial sarcoplasmic reticulum [18] as well as the transmembrane protein 43 [19], which function as a response element for PPAR gamma (peroxisome proliferator-activated receptor gamma), an adipogenic transcription factor which may explain the fibrofatty replacement of the myocardium. How

Table 1 Mutations in ARVC/D (OMIM™ Online Mendelian inheritance in man) (http://www.ncbi.nlm.nih.gov/Omim/)

ARVC/D type	Chromosome/locus	Gene codes	Mode of transmission
ARVC/D 1	14q23–q24	TGFβ-3	Autosomal dominant
ARVC/D 2	1q42–q43	RyR2	Autosomal dominant
ARVC/D 3	14q12–q22		Autosomal dominant
ARVC/D 4	2q32		Autosomal dominant
ARVC/D 5	3p23	Transmembrane protein 43	Autosomal dominant
ARVC/D 6	10p12–p14		Autosomal dominant
ARVC/D 7	10q22		Autosomal dominant
ARVC/D 8	6p24	Desmoplakin (DSP)	Autosomal dominant
ARVC/D 9	12p11	Plakophilin-2 (PKP2)	Autosomal dominant
ARVC/D 10	18q12	Desmoglein-2 (DSG2)	Autosomal dominant
ARVC/D 11	18q12.1	Desmocollin-2 (DSC2)	Autosomal dominant
ARVC/D 12	17q21	Plakoglobin (JUP)	Autosomal dominant
Naxos Disease	17q21	Plakoglobin (JUP)	Autosomal recessive

mutations of desmosomal protein genes cause the disease remains currently undetermined. It has been hypothesized that the loss of function of desmosomal protein may provoke detachment of myocytes at the intercalated discs and disrupt cell–cell adhesion, predisposing to fibrofatty degeneration, particularly under conditions of mechanical stress [11–13]. Other authors suggested a pathogenic role for viral infection that could be worsened by a mutant cardiac desmosome and contribute to disease pathogenesis [20, 21].

The role of inflammation in ARVC/D is unresolved, although inflammation may contribute to disease progression in ARVC/D. A study of Campian et al. [22] assessed cardiac inflammation non-invasively with the combined analysis of plasma inflammatory cytokine levels and cardiac ^{67}Ga scintigraphy, showing that ARVC/D patients had significantly higher plasma levels than controls of the pro-inflammatory cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-alpha as well as a significantly higher ^{67}Ga uptake in the right ventricular wall. The clinical implications of these findings remain to be clarified.

In an Italian study of 80 unrelated ARVC/D subjects undergoing genetic screening of all known ARVC/D genes showed that 13 individuals (16%) carried a desmoplakin mutation, 11 (14%) carried a plakophilin-2 mutation, 8 (10%) a desmoglein-2 mutation, and 2 (2.5%) a transforming growth factor (TGF 3) mutation [14]. Rampazzo et al. [11] identified a mutation in human desmoplakin domain (DSP) causing an autosomal dominant form of ARVC/D. Recessive mutations in DSP encoding desmoplakin have also been described in Carvajal syndrome, which consists of palmoplantar keratoderma, woolly hair, and arrhythmogenic right ventricular cardiomyopathy [23]. Naxos syndrome is an autosomal recessive variant of ARVC/D, in which affected individuals develop right ventricular cardiomyopathy (ARVC/D), skin (palmoplantar keratoderma), and hair abnormalities (woolly hair) due to homozygous mutations in the gene encoding junctional plakoglobin (JUP) mapped on chromosome 17 (locus 17q21) [12].

Calkins et al. [24] screened 38 family members of 12 desmosomal mutation-carrying ARVC/D subjects, which underwent genotyping and cardiac magnetic resonance imaging (CMR). Twenty-five individuals had mutations in PKP2, DSP, and/or DSG2 genes. RV abnormalities were associated with the presence of mutations and with disease severity. The only left ventricle (LV) abnormality detected, the presence of intramyocardial fat, was present in four individuals. Each of these individuals was a mutation-carrier, while one had no previously described ARVC/D-related abnormality.

Reports by Dalal et al. [25] and Van Tintelen et al. [26] confirm and extend previous observations by showing that PKP2 gene mutations are commonly found in ARVC/D patients, accounting for 40% of the cases. Furthermore, the study of Van Tintelen et al. indicates that in familial ARVC/D even the large majority (70%) is caused by PKP2 mutations. A systematic clinical evaluation of PKP-2 mutation carriers within families by Syrris et al. [27] demonstrated variable phenotypic expression, even among individuals with the same mutation. The data demonstrate that clinical expression of PKP2 mutations is heterogeneous even among first-degree relatives ranging from a complete lack of symptoms and/or clinical manifestations to a severe disease phenotype and exposed the limitations of the currently available diagnosis of ARVC/D.

The most comprehensive analysis of systematic desmosomal gene screening of five desmosomal genes in a population of patients with familial or sporadic forms of ARVC/D was published by Fressart et al. [28]. The presence of desmosomal mutations was associated with young age, symptoms, electrical substrate, and extensive structural damage, but not associated with familial context. DSG2 mutations were associated with more frequent left ventricular involvement ($p = 0.006$); moreover patients with multiple mutations were associated with more frequent sudden death ($p = 0.047$). Previous and new results support the use of molecular genetic testing with promising perspectives for early diagnosis of ARVC/D in relatives of patients with ARVC/D and for borderline index patients.

Symptoms

In the early phase, individuals are often asymptomatic but can be at risk of sudden cardiac death. Later individuals present with symptomatic arrhythmias, and right ventricular morphological abnormalities in conventional imaging. Disease progression may result in biventricular heart failure. According to Dalal et al. [29], the median age at presentation of disease is 29 years (interquartile range 20–36; range 2–63). The most common presenting symptoms are palpitations, syncope, and sudden cardiac death (SCD) in 27, 26, and 23% of patients, respectively. Cardiac arrest may also be the first manifestation of disease.

The most typical clinical presentation of ARVC/D is symptomatic ventricular arrhythmias of right ventricular origin, usually triggered by effort. Arrhythmias range from isolated premature ventricular beats to sustained ventricular tachycardia with left bundle branch block morphology and up to ventricular fibrillation leading to cardiac arrest [2]. Arrhythmias and electrocardiographic abnormalities can be present before histological evidence of myocyte degeneration or clinical presence of right ventricular dysfunction [30].

The progressive loss of the right ventricular myocardium can impair the function of the right ventricle and lead to severe pump failure. When ARVC/D involves the ventricular septum and the left ventricle, congestive heart failure occurs. Endocavitary mural thrombosis may develop within aneurysms or in the atrial appendages, when heart failure is complicated by atrial fibrillation leading to thromboembolism [31].

Diagnosis

Original International Task Force Criteria of ARVC/D were published in 1994 [6], are based on structural, histological, electrocardiography (ECG), arrhythmic, and familial features of the disease (Table 2), and were modified by Marcus et al. [32] in 2010. Abnormalities are divided into major and minor categories according to the specificity of their association with ARVC/D.

ECG findings in ARVC/D include T-wave inversions in V1–V3 in the absence of right bundle branch block (observed in 85% of ARVC/D patients), a cardinal feature of ARVC/D, and epsilon waves (in 33%), as well as a QRS duration >110 ms in V1 through V3 (present in 64% of patients).

Right precordial T-wave inversion is well recognized in ARVC/D, but has limited specificity because of its presence, such as in anterior ischemia or RV hypertrophy [32]. Arrhythmias of right ventricular origin are designated a minor criterion because of the occurrence in other diseases, particularly idiopathic RV outflow tract tachycardia. The strength of International Task Force Criteria of 1994 is that the criteria are usually specific, but they lack sensitivity and are largely qualitative rather than quantitative [33].

In the past, experience with ARVC/D has increased and additional diagnosis techniques, such as ECG markers, and mutation analysis as well as echocardiography and new imaging techniques, such as cardiovascular magnetic resonance tomography with late enhancement have been introduced. In a study of Quarta et al. [34], ECG features were investigated in a genotyped cohort with ARVC/D showing that 16 patients (23%) had changes during follow-up, with the appearance of new ECG abnormalities in seven (10%) and dynamic changes in nine patients (13%) without major structural or functional right ventricular abnormalities, suggesting an early stage of the disease. Four developed new and persistent T-wave inversion and eight had dynamic T-wave inversion in right precordial leads. Three developed new and another three had dynamic epsilon waves. As dynamic changes were not paralleled by

Table 2 Proposed clinical criteria for the diagnosis of ARVC/D [6]

	Major Criteria	Minor Criteria
Previous criteria for diagnosis of ARVC/D[a]		
I. Global or regional dysfunction/structural alteration[b]	• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment	• Mild global RV dilatation and/or ejection fraction reduction with normal left ventricle
	• Localised right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)	• Mild segmental dilatation of the RV
	• Severe segmental dilatation of the RV	• Regional right ventricular hypokinesia
II. Tissue characterization of walls	• Fibrofatty replacement of myocardium on endomyocardial biopsy	
III. Repolarization abnormalities		• Inverted T-waves in right precordial leads (V2 and V3) (people aged more than 12 yr; in absence of RBBB)
IV. Depolarization/conduction abnormalities	• Epsilon waves or localised prolongation (>110 ms) of the QRS complex in right precordial leads (V1–V3)	• Late potentials (signal averaged ECG)
V. Arrhythmias		• Left bundle branch block type VT (sustained and non-sustained) (ECG, Holter, exercise testing).
		• Frequent VES (more than 1,000/24 h) (Holter)
VI. Family history	• Familial disease confirmed at necropsy or surgery	• Familial history of premature sudden death (<35 years) due to suspected right ventricular dysplasia.
		• Familial history (clinical diagnosis based on present criteria)

RV right ventricle, *VES* ventricular extrasystole, *RBBB* right bundle branch block, *LV* left ventricle, *VT* ventricular tachycardia, *ECG* electrocardiogram

[a] Diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups

[b] Detected by echocardiography, angiography, magnetic resonance imaging, or radionuclide scintigraphy

progression of structural or functional right ventricular abnormalities, the study highlighted the importance of serial ECG evaluation in the diagnosis of individuals at risk of ARVC/D. A study proposed a criterion of prolonged S-wave upstroke in V1 through V3 $\geq$ 55 ms, which was the most frequent ECG feature in ARVC/D (95%) and correlated with the disease severity and induction of ventricular tachycardia (VT) on electrophysiological study [35].

Recently, modifications of the original Task Force Criteria have been proposed to make allowance for the advances in genetics and diagnostic modalities. In case of family members' modification of diagnosis criteria was proposed by Hamid et al. [36] to account for the broader spectrum of disease that is observed in family members. In first-degree relatives of a patient, confirmed to be affected by ARVC/D, the presence of right precordial T-wave inversion, or late potentials on signal-averaged ECG, or ventricular tachycardia with left bundle branch block morphology, or mild functional or morphological changes of the right ventricle on imaging, should be considered diagnostic for familial ARVC/D, as well the threshold of premature ventricular beats of 200 over 24 h in Holter monitoring (Table 3).

Original Task Force Criteria have been displayed by various authors to lack quantitative assessment of right ventricular global and regional abnormalities calling for modification of diagnostic criteria to better define the asymptomatic affected in systematic family screening and the asymptomatic or oligosymptomatic at high risk for syncope or cardiac arrest [37].

New task force criteria 2010

Marcus et al. [32] modified the International Task Force Criteria for the clinical diagnosis of ARVC/D to incorporate new knowledge and improve diagnostic sensitivity, while maintaining diagnostic specificity (Table 4). In this modification of the Task Force Criteria, quantitative criteria for the imaging studies are proposed and abnormalities are defined on the basis of comparison with normal subject data

In a first study of Cox et al. [38] applying new Task Force Criteria to patients suspected of ARVC/D, 64% of probable ARVC/D patients and 11% of family members were additionally diagnosed, suggesting that newly proposed Task Force Criteria could have a major impact in increasing diagnostic yield of ARVC/D.

Repolarization abnormalities are early and sensitive markers of disease expression in ARVC/D and reasonably specific in ARVC/D. T-wave inversion in V1, V2, and V3 and beyond in individuals >14 years of age who are otherwise healthy is observed in only 4% of healthy women and 1% of men [39].

Fat visualization on magnetic resonance imaging (MRI) cannot be defined as criteria, because it has not been found to be specific for ARVC/D [40] and has a poor inter-reader agreement. One possible reason for misinterpretation of the MRI study is that the original Task Force Criteria did not provide guidelines for the diagnosis of ARVC/D using MRI because the technology was just being introduced at that time [41].

According to Tandri et al. [42], non-invasive detection of right ventricular myocardial fibro-fatty changes in ARVC/D is possible by myocardial delayed enhancement-MRI (MDE-MRI). This method had excellent correlation with histopathology and predicted inducible VT on programmed electrical stimulation, suggesting a possible role in evaluation and diagnosis of patients with suspected ARVC/D.

Risk stratification and therapy

Patients with ARVC/D with a history of having been resuscitated from sudden cardiac death, patients with syncope, very young patients, and those who have marked right ventricular involvement are at the highest risk for arrhythmic death [43]. Also, the presence of left ventricular involvement is a risk factor. In a study of Turrini et al. [44], QRS dispersion ($\geq$40 ms) was the strongest independent

Table 3 Proposed Modification of Task Force Criteria for the Diagnosis of Familial ARVC/D [36]

Modified previous. ARVC/D in first-degree relatives plus one of the following:	
I. ECG	• T-wave inversion in right precordial leads (V2 and V3)
II. SAECG	• Late potentials seen on signal-averaged ECG
III. Arrhythmia	• LBBB type VT on ECG, Holter monitoring or during exercise testing
	• Extrasystoles >200 over a 24-h period (previously >1,000/24-h period in Task Force Criteria)
IV. Structural or functional abnormality of the RV	• Mild global RV dilatation and/or EF reduction with normal LV
	• Mild segmental dilatation of the RV
	• Regional RV hypokinesia

Table 4 Modified criteria for diagnosis of ARVC/D [32]

	Major criteria	Minor criteria
Modified criteria for diagnosis of ARVC/D		
I. Global or regional dysfunction/ structural alteration*	*By 2D echo*:	*By 2D echo*:
	• Regional RV akinesia, dyskinesia, or aneurysm	• Regional RV akinesia or dyskinesia
	• *and* 1 of the following (end diastole):	• *and* 1 of the following (end diastole):
	– PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2)	– PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2)
	– PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2)	– PSAX RVOT ≥32 to <36 mm (corrected for body size PSAX/BSA ≥18 to <21 mm/m^2)
	– *or* fractional area change ≤33%	–*or* fractional area change >33% to ≤40%
	By MRI:	*By MRI*:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
	• *and* 1 of the following:	• *and* 1 of the following:
	– Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)	– Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female)
	– *or* RV ejection fraction ≤40%	– *or* RV ejection fraction >40 to ≤45%
	By RV angiography:	
	• Regional RV akinesia, dyskinesia, or aneurysm	
II. Tissue characterization of walls	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60–75% by morphometric analysis (or 50–65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. 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 RBBB QRS ≥120 ms)	• Inverted T-waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete RBB) 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 RBBB
IV. Depolarization/conduction abnormalities	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T-wave) in the right precordial leads (V1 to V3)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
		• Filtered QRS duration (fQRS) ≥114 ms
		• Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
		• Root-mean-square voltage of terminal 40 ms ≤20 μV
		• Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete RBBB
V. Arrhythmias	• Non-sustained 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)	• Non-sustained 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 VES per 24 h (Holter)

Table 4 continued

	Major criteria	Minor criteria
VI. Family history	• 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[a] categorized as associated or probably associated with ARVC/D in the patient under evaluation	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<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 relative

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

RV right ventricle, *VES* ventricular extrasystole, *VT* ventricular tachycardia, *RBBB* right bundle branch block, *ECG* electrocardiogram, *LV* left ventricle, *PLAX* parasternal long-axis view, *RVOT* RV outflow tract, *BSA* body surface area, *PSAX* parasternal short-axis view, *aVF* augmented voltage unipolar left foot lead, *aVL* augmented voltage unipolar left arm lead

[a] 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

predictor of sudden death in ARVC/D. Syncope, QT dispersion >65 ms, and negative T-wave beyond V1 refined arrhythmic risk stratification in these patients.

Hulot et al. [45] developed a risk stratification scheme for cardiovascular death. High-risk patients present with clinical signs of right heart failure and/or have a left ventricular dysfunction, and have a history of ventricular tachycardia. They should be regarded as candidates for aggressive therapeutic management. Patients presenting without VT are at very low risk of cardiac events.

General conditions

Ventricular arrhythmias may be triggered by exercise leading to sudden death. Recently, Mutschelknauss et al. [46] reported on a 15-year-old girl with syncope during handball match caused by ventricular tachycardia. It is recommend that patients with ARVC/D avoid competitive athletics and that activity has to be limited to low intensity activities, such as walking [47].

Implantable defibrillators

The main decision in regard to management of ARVC/D concerns whether to implant an implantable cardiac defibrillator (ICD) for prevention of sudden death. Accepted indications for ICD implantation in ARVC/D include secondary prevention after prior cardiac arrest and VT with hemodynamic compromise [48, 49]. A large observational study by Corrado et al. [50] analysed the clinical impact of ICD therapy of patients with ARVC/D treated for prevention of sudden death showing that nearly half of the patients had at least one episode of ventricular tachyarrhythmia that required ICD intervention, despite antiarrhythmic drug therapy over a mean follow-up period of 3.3 years, and 24% experienced ventricular fibrillation/flutter that in all likelihood would have been fatal without termination by the device, suggesting a significant improvement in survival through the follow-up period. The study displayed also that history of either cardiac arrest or ventricular tachycardia with hemodynamic compromise, younger age, and left ventricular involvement are independent predictors of potentially lethal ventricular arrhythmias; patients who received an ICD because of either cardiac arrest or ventricular tachycardia with hemodynamic compromise experienced a high incidence of ventricular fibrillation/flutter (10% per year of follow-up) despite antiarrhythmic drug therapy confirming that they were ideal candidates for ICD therapy. Patients presenting with unexplained syncope derived much benefit from ICDs because of the similar annual rate of resuscitative ICD interventions (8% per year of follow-up). On the other hand, patients who received an ICD for ventricular tachycardia without hemodynamic compromise had a statistically significant better outcome with low rates of ventricular fibrillation/flutter during follow-up (3%), so that when taking into consideration, the side effects and complications of the ICD, it does not appear to be justified to implant an ICD in this subgroup of patients.

Piccini et al. [51] reported about experience with ICDs in 67 patients with definite or probable ARVC/D. Over a mean follow-up of 4.4 ± 2.9 years, 40 (73%) of 55 patients who met Task Force Criteria for ARVC/D and 4 (33%) of 12 patients with probable ARVC/D had

appropriate ICD therapies for VT/ventricular fibrillation ($p = 0.027$). 11 (39%) of 28 patients who received an ICD in the absence of a prior episode of sustained VT or VF and 33 (94%) of 35 patients who received an ICD for secondary prevention experienced appropriate ICD therapies ($p = 0.001$). Electrophysiologic testing did not predict appropriate ICD interventions in patients who received an ICD for primary prevention. Fourteen patients (21%) received ICD therapy for life-threatening arrhythmias (VT/VF >240 beats per minute). There was no difference in the incidence of life-threatening arrhythmias in the primary and secondary prevention groups. Based on these findings, Piccini et al. concluded that patients who meet the Task Force Criteria for ARVC/D are at high risk for sudden cardiac death and should undergo ICD placement for primary and secondary prevention, regardless of electrophysiologic testing results.

According to Wichter et al. [52], an ICD is imperative if an aborted sudden death had occurred. In case of sustained VT and/or syncope, ICD is also indicated in the presence of risk factors (extensive RV dysfunction, LV involvement, polymorphic VT, late potentials and epsilon wave, family history). If sustained VT as well as palpitations occurred in low risk patients (none of the previous risk factors), antiarrhythmic therapy and/or ablation are indicated, whereas syncope is reported as a distinct high risk factor, particularly in the young. Buja et al. [53] reported that patients with well-tolerated VT and localized right ventricular myocardial fibro-fatty substitution appear to have a good long-term prognosis, so that in this subgroup of patients, antiarrhythmic drugs and catheter ablation seem to be a reasonable first-line therapy.

Patients with arrhythmogenic right ventricular dysplasia presenting with ventricular fibrillation or haemodynamically unstable ventricular tachycardia have a high recurrence rate requiring appropriate ICD interventions [54]. Unfortunately, they often suffer from inappropriate ICD intervention, especially with sinus tachycardia and atrial fibrillation. Patients may benefit from an ICD with dual chamber detection algorithms to discriminate ventricular tachycardia from supraventricular tachycardia. The use of β-blockers and sotalol can also reduce the number of inappropriate interventions caused by sinus tachycardia or supraventricular tachyarrhythmias. In addition, by using lower detection rates as well as a single detection zone and by programming a higher ventricular tachyarrhythmia cut-off rate inappropriate ICD shocks can be avoided [55].

Potential complications of ICD therapy include perforation caused by thinning of the RV wall, difficulty in lead placement owing to inadequate R-wave amplitudes or high pacing thresholds and inadequate sensing or pacing during follow-up resulting from disease progression and deterioration of R-wave amplitudes and rising pacing thresholds; as well as failure to terminate ventricular arrhythmias owing to rising defibrillation thresholds over time resulting from disease progression [56]. These complications are more likely to occur in ARVC/D patients as a result of the replacement of RV myocardium with fat and fibrotic tissue. The data of Roguin et al. is somewhat reassuring, as the short-term and long-term risks of ICD therapy were similar to those in previous reports in non-ARVC/D patient populations. Psychiatric problems before implantation, life-shortening diseases ($\leq$6 months) are considered as relative contraindications to ICD implantation, as well as incessant ventricular tachycardia, in which catheter ablation is actually the appropriate therapy.

Many questions remain regarding ARVC/D. Because of the incomplete penetrance of the disease, long-term follow-up studies of family members are needed to determine the characteristics that predict progression to disease, as well as evaluation of which patients suspected of having ARVC/D require ICD implantation as primary prevention for sudden cardiac death. In the future, genetic testing may have a role in identifying patients at risk for sudden death [57]. The results of Hodgkinson et al. [58] support subsequent prophylactic ICD implantation as a primary prevention therapy in familial ARVC with a high-risk DNA haplotype (ARVC/D 5, 3p25) and/or pedigree position with a beneficial impact on survival in males in this population. The 5-year mortality rate after ICD implantation in males was zero when compared with 28% in control subjects ($p = 0.009$).

Antiarrhythmic agents

Not much data are available concerning the use of pharmacologic agents in the treatment of patients with ARVC/D for the prevention of sudden cardiac death. A study of Hiroi et al. [59] suggests that carvedilol is not only useful for controlling arrhythmia but also for improving left ventricular function in some patients with ARVC/D. If this is inadequate to control symptoms or to prevent recurrent VT, membrane active antiarrhythmic agents, such as sotalol and, if necessary, amiodarone should be considered. According to data of Wichter et al. [60] sotalol proved to be highly effective in patients with ARVC/D and inducible as well as non-inducible ventricular tachycardia with an efficacy of 68.4% and respectively 82.8%; if sotalol is ineffective in inducible ventricular tachycardia response to other antiarrhythmic drugs is unlikely and therefore non-pharmacological therapy without further drug testing should be considered. In this study amiodarone did not prove to be more effective than sotalol and may not be an alternative because of frequent side effects during long-term therapy, especially in young patients. Verapamil and β-blockers were effective in a considerable number of

patients with non-inducible ventricular tachycardia and may be a therapeutic alternative in this subgroup. Class I agents appear to be rarely effective in the treatment of both inducible and non-inducible ventricular tachycardia in arrhythmogenic right ventricular disease.

In a recent cohort of ARVC/D subjects with implantable cardioverter-defibrillators (ICDs) enrolled in the North American ARVC/D Registry, neither beta-blockers nor sotalol seemed to be protective against clinically relevant ventricular arrhythmias [61]. Amiodarone, although only received by a relatively small number of patients, had the greatest efficacy in preventing ventricular arrhythmias. As exemplified by this study and the fact that no deaths occurred in the high risk patients over an average of more than 1 year of follow-up, ICDs appear to be effective in preventing death in ARVC/D patients.

Catheter ablation

Indications for catheter ablation in subjects with ARVC/D include monomorphic and well-tolerated VT with localized forms of the disease and drug-refractory or incessant VT or frequent ICD discharges. The current mapping and ablation techniques include activation and entrainment mapping during tolerated VT and substrate ablation using three-dimensional electroanatomic mapping systems [62].

The role of electrophysiological studies and VT catheter ablation in ARVC/D remain poorly defined, and is frequently used as a palliative measure for patients with refractory VT. The progressive pathology of ARVC/D suggests that catheter ablation would not be a long-term curative procedure [63]. Dalal et al. reported on a cohort of 24 patients which underwent 48 ablation procedures at 29 different electrophysiology centers in the United States [64]. The cumulative VT free survival was 75% at 1.5 months, 50% at 5 months, and 25% at 14 months. The immediate success of the procedure had no bearing on recurrence, nor did the use of an assistive mapping technique, or repetition of the procedure.

In a study of Miljoen et al. [65], three-dimensional electroanatomical mapping was performed in 11 patients with well-tolerated sustained ventricular tachycardia and ARVC/D. Detailed three-dimensional electroanatomical mapping was able to identify peritricuspid ventricular reentry which is a frequent mechanism of ventricular tachycardia (VT) in patients with ARVC/D and to help in guiding radiofrequency ablation in patients with ARVC/D especially in patients exhibiting a reentrant mechanism of their ventricular tachycardia.

Substrate-based mapping and ablation of VT are feasible in ARVC/D patients in whom conventional mapping during tachycardia is not possible [66]. This method may achieve a high short-term success rate, but recurrences become increasingly common over the long term, possibly as a result of the progressive nature of this disease.

Cardiac transplantation

Orthotopic heart transplantation is considered in patients with progressive heart failure and intractable recurrent ventricular arrhythmias [67]. It must always be considered in advanced cases of ARVC/D with malignant arrhythmias or refractory congestive heart failure with or without uncontrolled arrhythmias, because it is the only way to remit the symptoms and the disease [68].

Conflict of interest None.

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