

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/DYSPLASIA

Definition

Arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC) is predominantly a genetically determined heart muscle disorder that is characterized by fibrofatty replacement of the right ventricular myocardium. This results in abnormalities ranging from regional wall motion abnormalities and aneurysms to global dilation and dysfunction, with or without left ventricular involvement.¹⁻⁴ ARVC is the best characterized of the Arrhythmogenic Cardiomyopathies.⁵

Epidemiology

The estimated prevalence of ARVC in the general population ranges from 0.02 to 0.08%.^{1, 2, 4, 6} ARVC is one of the most arrhythmogenic form of human heart disease, and a major cause of sudden death in the young.⁷ The disease is typically transmitted with an autosomal dominant pattern of inheritance, although rare autosomal recessive forms have been described.¹

Aetiology

ARVC is most often familial, with autosomal dominant inheritance.⁸ Five causative desmosomal genes (encoding for proteins of the cell adhesion complex) have been identified, but since only 30-50% of patients have one of these gene abnormalities, it is assumed that there are other genes not yet identified. Frequently patients with ARVC have more than one genetic defect in the same gene (compound heterozygosity) or in a second complementary gene (digenic heterozygosity).⁹ In addition, a family member may have an ARVC gene defect and develop the disease or have no or minimal manifestations of the disease.⁹ ARVC is usually inherited as an autosomal dominant trait with variable, age-dependent penetrance, meaning that the risk of a family member inheriting an abnormal gene is 50% for all offspring of the genetically affected proband. Up to 16 genes have been associated with the ARVC/D phenotype.³ The main responsible genes are presented in Table 1 and Figure 1. There are also recessive forms such as Naxos disease (palmoplantar keratosis, wooly hair and ARVC/D due to plakoglobin mutations), and Carvajal syndrome, that are associated with a cutaneous phenotype (desmoplakin mutations).² A novel *desmin p.Glu401Asp* mutation causes predominant inherited left ventricular arrhythmogenic cardiomyopathy/dysplasia with a high incidence of adverse clinical events in the absence of skeletal myopathy or conduction system disorders.¹⁰ **Desmoplakin** cardiomyopathy is a distinct form of arrhythmogenic

cardiomyopathy characterized by episodic myocardial injury, left ventricular fibrosis that precedes systolic dysfunction, and a high incidence of ventricular arrhythmias.¹¹

Extradesmosomal gene mutations have also been described. In a recent extensive study in Dutch families, mutations mainly affected placophilin-2 (truncating PKP2 mutations).¹² **PKP2 (plakophilin)** variants that reduce the sodium current may also yield a Brugada syndrome phenotype.¹³ LMNA (encoding for lamin proteins A and C), and **TMEM43** (encoding for the nuclear protein LUMA) mutations have also been found in severe forms of ARVC thus indicating that it is not just a disease of desmosomal proteins.¹⁴

¹⁵ In addition, **DES-encoding desmin**, **TTN-encoding titin**, and **PLN-encoding phospholamban** have been suggested as novel ARVC genes.² Mutations in **RYR2** gene encoding the ryanodine receptor have been reported in ARVC in patients with an arrhythmic presentation resembling that of catecholaminergic polymorphic ventricular tachycardia.¹⁶ However, they may all account for overlap syndromes characterized mostly by a dilated cardiomyopathy phenotype, and a high prevalence of conduction disease. The exact role of inflammatory (viral myocarditis) or immune mechanisms that may be present is not known.

Compared with other familial cardiomyopathies and ion channelopathies associated with sudden death, arrhythmogenic cardiomyopathy has low penetrance and unusually variable disease expression, even within members of the same family who carry the same disease-associated presumably due to genetic and/or epigenetic modifiers that interact with environmental factors.⁶ Thus, ARVC does not appear to be a monogenic disease, but rather a complex genetic disease, characterized by marked intrafamilial and interfamilial phenotype diversity.

Presence of organ-specific anti-heart autoantibodies and anti-intercalated disk autoantibodies provides evidence of autoimmunity in the majority (85%) of familial pedigrees and in almost half (45%) of sporadic arrhythmogenic right ventricular cardiomyopathy pedigrees. In probands and in affected relatives, these antibodies were associated with disease severity features.¹⁷

Pathophysiology

ARVC is mainly affecting proteins of the intercalated disc, particularly the desmosomes that are responsible for the mechanical coupling of myocytes. Desmosomes are large intercellular junctional protein complexes that primarily serve to link intermediate filaments to the plasma membrane, and create strong intercellular linkages (intercellular cardiac glue) that allow transmission of force through the cardiac syncytium.¹⁸ Intercellular junctions are composed of a core region, which mediates cell to cell adhesion, and a plaque region which provides attachment to the intermediate filament cytoskeleton. Three separate groups of proteins assemble to form desmosome: transmembrane proteins, ie desmosomal cadherins such as

desmoglein and desmocollin, desmoplakin, a plakin family protein that binds directly to intermediate filaments, and linker proteins, ie armadillo proteins such as plakoglobin and plakophilin which mediate interactions between the desmosomal cadherin tails and desmoplakin.¹

The lack of the protein or the incorporation of defective proteins into cardiac desmosomes provokes detachment of myocytes at the intercalated discs, particularly under mechanical stress conditions. Histologically, there is presence of replacement-type fibrosis and myocyte degenerative changes together with substantial fat replacement (Figure 2). The replacement of the right ventricular myocardium by fibrofatty tissue is progressive, starting from the epicardium or midmyocardium and then extending to become transmural. It eventually leads to wall thinning and aneurysms, typically located at the inferior, apical, and infundibular walls (so-called triangle of dysplasia), the hallmark of ARVC.^{2, 6} The fibrofatty replacement interferes with electrical impulse conduction, and is the key cause of epsilon waves, right bundle branch block, late potentials, and reentrant ventricular arrhythmias also possibly due to gap junction remodeling.

Left ventricular involvement, usually at the posterobasal and antrolateral wall, is detected by autopsy in most patients, with isolated right ventricular disease seen in 13%, isolated left ventricular disease in 17%, and biventricular involvement in 70% of them.¹⁹ It presents with a preferential involvement of the lateral and postero-lateral basal LV and is associated mostly with variants in desmoplakin and desmoglein-2 genes.²⁰ Thus, the term ARVC refers to RV, biventricular and LV dominant subtypes. With the identification of desmosomal disease-causing variants, individuals and families with predominantly LV arrhythmia and structural abnormalities were recognized, as were patients with nondesmosomal arrhythmia-associated variant (eg, lamin A/C, phospholamban, filamin-C who had arrhythmogenic cardiomyopathy with predominantly left (but also right) or biventricular phenotypes.⁸

Mechanical stress may impact cellular junctions and exercise may exacerbate the progression of the disease, and predispose to sudden cardiac death.^{18, 19} Sudden cardiac death attributable to ARVC affects men predominantly, most commonly occurring during exertion in athletic individuals in the absence of previous reported cardiac symptoms.¹⁹

Presentation

Patients usually present between the second and fourth decades of life due to palpitations or effort-induced syncope. Ventricular ectopic beats or runs of ventricular tachycardia occur early in the natural history of arrhythmogenic cardiomyopathy, often preceding structural remodeling of the myocardium, and sudden death by VF may also be seen in the asymptomatic young people and athletes. Identification of AF or VT is associated with an

adverse prognosis.²¹ Presentation with SCD or VF occurs at a younger age compared to sustained monomorphic VT,²² and there is a predilection for the male sex.² Patients with ARVC may present with asymptomatic NSVT despite only subtle RV abnormalities, and have a trend for an increased arrhythmic risk and a rate of appropriate ICD intervention of 3.7%/year.²³ Left ventricular-sided arrhythmias may also be seen.²⁴ Disease progression may occur during exacerbations that are, usually, clinically silent or characterised by the appearance of life-threatening arrhythmias and chest pain. Environmental factors, such as exercise or inflammation, might facilitate disease progression. Progressive heart failure may occur in <10% of patients.²⁵

Investigations

Diagnostic criteria for ARVC are presented in Table 2. Clinical diagnosis of ARVC may be difficult due to the broad spectrum of phenotypic manifestations, ranging from severe to concealed forms.²⁶

ECG depolarization abnormalities result from delayed right ventricular activation and include RBBB, prolongation of right precordial QRS duration (110 ms or more), and epsilon waves, defined as small amplitude potentials occurring after the QRS complex and before the onset of the T waves (Figure 3). The presence of epsilon waves should be evaluated with caution, especially in patients without other diagnostic criteria.²⁶ Rarely, post-QRS deflections in post-infarction scars may simulate epsilon waves.²⁷ Usually patients have inverted T waves over V₁-V₃, but when anterior TWI is preceded by J-point elevation ≥ 0.1 mV, the likelihood of ARVC is extremely low.²⁸ Negative T waves in leads V₁ and V₂ may be a normal variant. S wave duration >55 ms in V₁-V₃ is also a marker of the disease. Inverted T waves or epsilon waves in inferolateral leads suggest biventricular involvement.²⁹ Low QRS voltages (<0.5 mV) in the limb leads can be an ECG marker predictive of LV involvement.²⁶ Prolonged terminal activation duration (TAD) is discussed in Differential Diagnosis. Pathological Q waves, left posterior fascicular block, and a prominent R-wave in V₁ are common ECG signs in arrhythmogenic left ventricular cardiomyopathy.³⁰

Late potentials identified by **signal averaged ECG** constitute a minor diagnostic criterion (Table 4), but its use has declined due to its limited sensitivity and specificity.⁸

Exercise testing in asymptomatic PKP-2 mutation carriers may reveal new epsilon waves, premature ventricular contractions with superior axis, and new terminal activation duration ≥ 55 ms (Figure 4).³¹

Holter monitoring may reveal ventricular ectopic beats or runs of VT with LBBB morphology and inferior or superior axis. RBBB VT occurs in 17% of cases, with most RBBB VTs (62%) originating from the RV.³² Non-sustained VT or >500 PVCs/24h on Holter precede structural abnormalities that are detected by CMR.³³ Annual ambulatory ECG

monitoring is recommended in patients with ARVC to aid in diagnosis, management, and risk stratification (Table 3).

On **echocardiography** the more common structural changes in the right ventricle consist of wall motion abnormalities, trabecular derangement, and diastolic dilatation of the RVOT, but the ventricle may be normal in mild forms of ARVC. Typically, the inferior-subtricuspid, antero-apical, and mid-outflow tract regions are affected (triangle of dysplasia). In the early stages of ARVC, overall right ventricular function may be normal with local or regional wall motion abnormalities, and these are difficult to quantify.³⁴ As the disease progresses RV dilatation and failure may occur. Lateral and posterolateral left ventricular involvement may also occur.^{19, 20} Although ARVC was originally described as a right ventricular disease, it is now recognized to include a spectrum of biventricular and left-dominant forms that may be misdiagnosed as dilated cardiomyopathy. The presence of any LV systolic dysfunction in desmoplakin cardiomyopathy (LVEF <55%), particularly when associated with frequent premature ventricular contractions and/or LV myocardial late gadolinium enhancement, indicates a substantial risk for severe ventricular arrhythmias.¹¹

Cardiac magnetic resonance is the preferred imaging technique by means of detecting fatty tissue and, with gadolinium, intramyocardial fibrosis.²⁶ This is very important, since intramyocardial fat without fibrosis is present in the right ventricular anterolateral and apical region even in a normal heart and increases with age and bodyweight.³⁵ Thus, caution is needed in patients with misdiagnoses of ARVC mostly based on cardiac imaging/CMR features.³⁶ However, CMR abnormalities are indicative of high risk in the presence of ECG and/or Holter abnormalities.³³ CMR-detected circumferential RV strain and global longitudinal strain are emerging tools under study. When CMR is not feasible, 4D-cine imaging by multidetector cardiac computed tomography is also a promising tool.³

Isoproterenol testing has been found very sensitive for diagnosis of ARVC. Continuous infusion of isoproterenol (45 µg/min) is given for 3 minutes, and induction of polymorphic premature ventricular contractions with ≥1 couplet or sustained or nonsustained ventricular tachycardia with LBBB configuration indicates ARVC.³⁷

Electrophysiology study is useful for differential diagnosis between ARVC and idiopathic right ventricular outflow tract tachycardia, but the role of inducibility of sustained VT or VF for prediction of long-term arrhythmic outcome in ARVC patients is debatable.³⁸

Electroanatomical mapping can reveal low voltage areas either endocardially or epicardially that correspond to fibrofatty myocardial replacement, and could assist in the differential diagnosis with idiopathic right ventricular outflow tract tachycardia.³⁹ However, it is not proposed for routine diagnosis.²⁶

Endomyocardial biopsy is not indicated because the structural changes in ARVC tend to spare the subendocardium and do not typically involve the interventricular septum. The 2021

GL on HF recommend that it should be reserved to highly selected cases after all non-invasive studies have been assessed.⁴⁰ Fibrofatty replacement with or without replacement type fibrosis at RV septal biopsies are the characteristic findings. Endomyocardial biopsy has low sensitivity for the diagnosis in cases of focal distribution.

Immunohistochemical analysis of endomyocardial biopsy samples has been found a sensitive and specific diagnostic test for ARVC by means of detecting defective desmosomal proteins at intercalated discs.⁴¹ However, this diagnostic finding cannot discriminate ARVC from granulomatous myocarditis including cardiac sarcoidosis.⁴²

Antibodies against desmoglein-2 have also been reported as a sensitive and specific biomarker for ARVC, but experience is limited.⁴³

Differential diagnosis

The differential diagnosis of ARVC is presented in Table 4. The diagnosis of ARVC should be considered in the following: patients with exercise related palpitations and/or syncope; survivors of sudden cardiac arrest (particularly during exercise); and individuals with frequent ventricular premature beats (>500 in 24 hours) and/ or VT of LBBB morphology in the absence of other heart disease.⁸ Differential diagnosis is aimed at exclusion of **idiopathic right ventricular outflow tract tachycardia** that is benign and displays LBBB morphology with inferior axis. Patients with idiopathic RVOT-VT have a normal 12-lead ECG, normal imaging tests. The absence of ECG repolarisation and depolarisation abnormalities and of right ventricular structural changes, recording of a single VT morphology and non-inducibility at programmed ventricular stimulation, and a normal voltage map provide evidence for the idiopathic nature of the VT.⁶ A septal origin of VT is significantly more often observed in idiopathic RVOT-VT than in ARVC which usually affects the RV free wall and spares the septum. A single LBBB/inferior axis VT morphology favours the diagnosis of idiopathic RVOT-VT, while multiple VT morphologies, either spontaneous or induced, strongly suggest ARVC.²⁶ Prolonged terminal activation duration (TAD) is measured from the nadir of the S wave to the end of all depolarization deflections. A TAD ≥ 55 ms in any of the V1–V3 leads in the absence of complete RBBB differentiates ARVC from right ventricular outflow tract (RVOT)-VT (Figure 5).⁸ QRS duration in lead I of >120 ms, earliest onset QRS in lead V1, QRS notching, and a transition of V5 or later predict the presence of ARVC (Figure 6).⁴⁴ QRS notching in multiple leads was defined as a QRS complex deflection on the upstroke or downstroke of ≥ 0.05 mV that did not cross baseline occurring in at least 2 leads (Figure 7). A score ≥ 5 suggests ARVC. A QRS duration of ectopic beats >180 ms also indicates ARVC rather than normal heart RVOT ectopy.⁴⁵ Differences between **dilated cardiomyopathy vs. left-dominant ARVC** are presented in

Tables 5 and 6.^{26, 46} Older age of symptom onset, presence of cardiovascular comorbidities, nonfamilial pattern of disease, PR interval prolongation, high-grade atrioventricular block, significant left ventricular dysfunction, myocardial delayed enhancement of the septum, and mediastinal lymphadenopathy should raise the suspicion for **cardiac sarcoidosis**.⁴⁷

Differences with **Brugada syndrome** are presented in Table 7. In **black athletes** without concomitant symptoms or family history, T-wave inversion and RV enlargement may be a benign finding.⁴⁸ **Left-to right shunts, valve disease** and malformations such as **Uhl's anomaly** and **ventricular aneurysms** or **diverticulae** should also be considered as other causes of right heart dilatation.²⁶

Genetic Testing

The estimated overall rate of successful genotyping among patients meeting the diagnostic criteria for ARVC established by the international task force is approximately 50%.¹

Molecular genotyping is currently applied to relatives of a proband with a known mutation probably associated with ARVC for risk assessment (presymptomatic test), while it is not routinely used in isolated cases with a borderline phenotype for confirming the diagnosis.⁹ A negative genetic test does not exclude the possibility that the phenotype is due to a mutation of unknown and thus untested disease-causing genes. Approximately 50% of ARVC/D probands do not carry any known causative gene mutations.⁴⁹ The certainty of detecting causative mutation carriers is further limited by the difficulty in distinguishing causative mutations (mostly missense gene variants) from polymorphisms as well as by the potential presence of an undetected second pathogenetic mutation in the same or another gene. There is a low signal-to-noise ratio with mutations in a recent series identified in 43% of ARVC cases and in 16% of controls.⁵⁰ Radical mutations in apparently healthy subjects are high-probability ARVC-associated mutations, whereas rare missense mutations should be interpreted in the context of race and ethnicity, mutation location, and sequence conservation.⁵⁰ There is no evidence that the genotype may help with management strategies.

It has been shown, however, that almost one-third of at-risk relatives have electrical progression that precedes detectable structural changes that are rare.^{51, 52} The limitations of current understanding of the genetic basis of ARVC and the high genetic noise due to frequent disease associated genetic variants both in the normal population and other cardiomyopathies are associated with the risk of misdiagnosis if molecular genetic results are integral part of the diagnostic scoring system.²⁶ Recommendations are presented in Table 7.

Risk stratification

The annual incidence of SCD is not known, with reported rates ranging from 0.08 to 3.6%,¹ although in ICD recipients the annual rate of intervention is up to 5%.^{7, 23} These data are derived from studies on high-risk patients; studies of community-based patient cohorts have shown an annual mortality <1% for treated index patients and family members.⁵³ Electrical instability by means of AF, frequent PVCs, and sustained monomorphic VT, syncope, the presence of multiple mutations or a mutation in TMEM43, participation in strenuous exercise after the diagnosis of ARVC, and male sex predict lethal arrhythmias at follow-up.^{19, 21, 54} However, in the North American ARVC Registry, the only risk factors for ventricular arrhythmias were spontaneous ventricular arrhythmias before enrollment and a younger age at ICD implantation.⁵⁵ In a retrospective cohort from US and European centres, among only 4 predictors, younger age, male sex, premature ventricular complex count, and number of leads with T-wave inversion, were associated with life-threatening ventricular arrhythmias.⁵⁶ A prediction model based on age, sex, cardiac syncope in the prior 6 months, non-sustained ventricular tachycardia, number of premature ventricular complexes in 24 h, number of leads with T-wave inversion, and right ventricular ejection fraction has been derived from data of big databases with ARVC.⁵⁷ A correction to the 2019 ARVC risk calculator was proposed,⁵⁸ but it may overestimate the risk.⁴ Cardiac arrest due to VF can occur at any time during the disease course. The value of programmed ventricular stimulation is debatable with both negative,³⁴ and positive³⁹ results reported. Family history is of rather limited value in predicting SCD.²³ Whereas LV involvement has been considered for a long time as an expression of the advanced disease phase, it is now accepted that ARVC can start with isolated or predominant LV involvement since the early stages.^{2, 19} The genotype of ARVC mutation carriers impacts clinical course on the clinical course and disease expression.²² Desmosomal mutations, particularly for plakophilin(*PKP2*), are an important risk factor for ventricular arrhythmic events.⁵⁹ Pathogenic desmoplakin(*DSP*) gene variants are associated with a high risk for sustained ventricular arrhythmia.⁶⁰ The DSP risk score is a novel model that leverages readily available clinical parameters to generate individualized assessments of VA risk in patients with P/LP *DSP* variants (Figure 8).⁶¹

Therapy

Asymptomatic patients or healthy gene carriers do not require prophylactic treatment. They should undergo cardiac follow-up, including medical history, 12-lead ECG, 24-h Holter monitoring, exercise testing, and echocardiography on a regular basis. The role of antiarrhythmic therapy is limited.²¹ **Amiodarone** has been shown to prevent ventricular arrhythmias more effectively than beta blockers in ARVC patients treated with ICD.⁶²

Sotalol at high doses (320-480 mg daily) has also been found partially effective,⁶³ and **beta blockers** should, theoretically at least, be efficacious (Table 8).³⁸ Inhibition of the ryanodine 2 receptor via the use of **flecainide** may also be helpful. In an observational study, flecainide use had a favorable safety profile and was associated with an observed to a significant reduction in arrhythmic burden in patients with ARVC, irrespective of the underlying genotype or LV involvement. Proarrhythmic effects were detected in 4% of patients.⁶⁴ Treatment with **ICD** is indicated in patients with cardiac arrest, syncope, or haemodynamically poorly-tolerated VT, or one or more risk factors for SCD (Table 8 and Figure 9).^{65 38} 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 (estimated rate, 3.7% per year).¹

The majority of VT in ARVC are monomorphic, and antitachycardia pacing is highly successful in terminating VT independent of its cycle length. Thus, all ICDs should be programmed for antitachycardia pacing.⁵⁵ A potential problem with ICD in ARVC is that the disease is often progressive, leading to loss of myocardium and reduced ventricular R-wave sensing over time. **Catheter ablation** of VT (endocardial or epicardial), when feasible, is successful in reducing further episodes,³⁸ but cannot offer absolute protection without ICD backup since the progressive course of the disease precludes any curative role. Heart failure is treated according to standard recommendations. **Cardiac transplantation** may be needed in patients with intractable arrhythmias or heart failure.

A follow-up by non-invasive clinical evaluation of healthy gene carriers or children with unknown genotype who have a positive family history of ARVC should be performed on a regular basis after puberty (every 1–2 years) to monitor for disease onset and progression.²⁶

Physical activity is restricted to mild cardiovascular sports for weight management with a low static component (Table 9). Competitive sports are prohibited, being associated with a two-fold increased risk of ventricular arrhythmias and/or sudden death; recreational sports may be allowed.^{8, 66-69}

Pregnancy

It is well tolerated but clinical follow-up is recommended in the last trimester and puerperium, because of a reported increased risk of ventricular arrhythmias. Drug therapy may be indicated (Table 10).

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