ARRHYTHMOGENIC CARDIOMYOPATHY

Definition

Arrhythmogenic cardiomyopathy (ACM) has been defined as an arrhythmogenic heart muscle disorder not explained by ischemic, hypertensive, or valvular heart disease.[1] The term indicates a group of inheritable cardiomyopathies characterized by ventricular scarring and/or fibro-fatty replacement, and associated with a significant risk of sudden cardiac death due to ventricular arrhythmias.[2, 3] ***Arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC)*** is the most typical form of ACM, characterized by fibrofatty replacement of the right ventricular myocardium. [2] This results in abnormalities ranging from regional wall motion abnormalities and aneurysms to global dilation and dysfunction, with or without left ventricular involvement.[4-7]

Epidemiology

The incidence of ACM varies extensively by geographical area.[2] However, the estimated prevalence of ARVC, in particular, in the general population ranges from 0.02 to 0.05%.[4, 5, 7] ARVC is one of the most arrhythmogenic form of human heart disease, and a major cause of sudden death, especially in young patients and endurance athletes.[8] The disease is typically transmitted with an autosomal dominant pattern of inheritance, although rare autosomal recessive forms have been described.[4]

Aetiology

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.[1, 2, 6] Up to 16 genes have been associated with the ARVC phenotype,[6] but the main responsible genes are mostly desmosomal, encoding for proteins of the cell adhesion complex (Table 1 and Figure 1). However, since only 30-50% of patients have one of these gene abnormalities, it is assumed that there are other genes not yet identified. There are also recessive forms such as ***Naxos disease*** (palmoplantar keratosis, wooly hair and ARVC due to plakoglobin mutations), and ***Carvajal syndrome***, that are associated with a cutaneous phenotype (desmoplakin mutations).[5] *Filamin C (FLNC)* variants and a novel *desmin mutation* cause 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.[2, 9] *Desmoplakin* cardiomyopathy is an aggressive form of arrhythmogenic cardiomyopathy characterized by

episodic myocardial injury, left ventricular fibrosis that precedes systolic dysfunction, and a high incidence of ventricular arrhythmias.[10] *PKP2 (plakophilin)* are the most common genetic variants associated with ARVC but they reduce the sodium current and may also yield a Brugada syndrome phenotype.[11] *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.[12] [13] 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.[14] However, they may all account for overlap syndromes characterized mostly by a dilated cardiomyopathy phenotype, and a high prevalence of conduction disease. Inflammatory (viral myocarditis) and/or immune mechanisms may also play a role.

Pathophysiology

As with all forms of genetically based cardiovascular disease, the mechanisms responsible for the phenotype that develops rely on dysfunction of final common protein pathways.[1] These "final common pathways" can interact as overlapping pathways through protein-protein binding and, in these cases, can provide complex phenotypes, such as dilated cardiomyopathy (DCM) with significant arrhythmia potential. In the UK Biobank, approximately1 of 6 of adults with putative pathogenic variants in DCM genes exhibited early DCM features potentially associated with DCM genotype, most commonly manifesting with arrhythmias in the absence of substantial ventricular dilation or dysfunction.[15] Although rare, ACM can also overlap with hypertrophic cardiomyopathy (HCM; final common pathway, the sarcomere), restrictive cardiomyopathy (RCM; final common pathway, the sarcomere), or LV noncompaction (LVNC; final common pathway, the sarcomere and cytoskeleton). Troponin T variants, unlike other sarcomeric disease-causing genes, may present with cardiac arrest or sudden death despite mild or even absent LV hypertrophy, whereas troponin I variants may cause a restrictive phenotype in which the dominant clinical presentation is atrial fibrillation. Nonsarcomeric HCM (eg, Anderson-Fabry disease), caused by alpha-galactosidase A variants, may also initially present with arrhythmia, though not in the absence of diagnostic phenotypic features. Mitochondrial diseases are heritable conditions caused by genetic variants in the mitochondrial or nuclear DNA (prevalence 1 in 5,000 individuals), resulting in dysfunction of the mitochondrial respiratory chain and abnormal ATP production. Cardiac involvement is common with left ventricular hypertrophy, arrhythmias and conduction disease, Wolff-Parkinson-White syndrome, and dilated cardiomyopathy being the most frequently reported manifestations. [16]

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.[17] 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.[4]

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.[5, 18] 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.[1]

Mechanical stress may impact cellular junctions and exercise may exacerbate the progression of the disease, and predispose to sudden cardiac death.[17, 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]

Among other drivers and modulators of phenotype, inflammation in response to viral infection and immune triggers have been postulated to be an aggravator of cardiac myocyte damage and necrosis.[21] 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.[22]

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.[23] Presentation with SCD or VF occurs at a younger age compared to sustained monomorphic VT,[24] and there is a predilection for the male sex.[5] 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.[25] Left ventricular-sided arrhythmias may also be seen.[26] 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.[27]

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.[28]

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.[28] Rarely, post-QRS deflections in post-infarction scars may simulate epsilon waves.[29] Usually patients have inverted T waves over V_1-V_3, but when anterior TWI is preceded by J-point elevation ≥0.1 mV, the likelihood of ARVC is extremely low.[30] Negative T waves in leads V1 and V2 may be a normal variant. S wave duration >55 ms in V_1-V_3 is also a marker of the disease.

Inverted T waves or epsilon waves in inferolateral leads suggest biventricular involvement.[31] Low QRS voltages (<0.5 mV) in the limb leads can be an ECG marker predictive of LV involvement.[28] 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.[32]

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.[1]

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).[33]

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.[34] Non-sustained VT or >500 PVCs/24h on Holter precede structural abnormalities that are detected by CMR.[35] 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.[36] As the disease progresses RV dilatation and failure may occur. Lateral and posterolatral left ventricular involvement may also occur.[19, 20] Although ARVC was originally described as a right ventricular disease, it is now recognizd 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.[10]

Cardiac magnetic resonance is the preferred imaging technique by means of detecting fatty tissue and, with gadolinium, intramyocardial fibrosis.[28] 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.[37] Thus, caution is needed in patients with misdiagnoses of ARVC mostly based on cardiac imaging/CMR features.[38] However, CMR abnormalities are indicative of high risk in the presence of ECG and/or Holter abnormalities.[35] 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.[6]

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.[39]

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.[40]

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.[41] However, it is not proposed for routine diagnosis.[28]

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.[42] 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.[43] However, this diagnostic finding cannot discriminate ARVC from granulomatous myocarditis including cardiac sarcoidosis.[44]

Antibodies against desmoglein-2 have also been reported as a sensitive and specific biomarker for ARVC, but experience is limited.[45]

In patients with suspected ACM who do not meet the diagnostic criteria for ARVC, the evaluation should be systematic to establish the diagnosis of other genetic and nongenetic forms of ACM. The pedigree evaluation should include a 3-generation family tree with an emphasis on premature cardiovascular events (eg, sudden death, HF) and associated cardiac (eg, arrhythmias, conduction disease) and noncardiac (eg, skeletal myopathy, renal failure, auditory/visual defects) phenotypes.[1]

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.[1] 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.[18] 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.[28] 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).[1] 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).[46] QRS notching in multiple leads was defined as a QRS complex deflection on the upstroke or downstroke of 4 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.[47] Differences between ***dilated cardiomyopathy vs. left-dominant ARVC*** are presented in Tables 5 and 6.[28, 48] 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***.[49] 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.[50] ***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 dilartation.[28]

Genetic Testing

The estimated overall rate of successful genotyping among patients meeting the diagnostic criteria for AVRC established by the international task force is approximately 50%.[4] Thus, about 40% of all ACM patients remain gene-elusive, even when large panel next generation sequencing or exome/genome sequencing is employed.[2] 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. 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. 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.[28] Furthermore, in almost all probands, the first trigger of a clinical evaluation (which usually precedes genetic testing) is the presence of a phenotype or an arrhythmic event.[2] Recommendations for genetic testing 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%,[4] although in ICD recipients the annual rate of intervention is up to 5%.[8, 25] 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.[51] 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, 23, 52] 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.[53] 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.[54] 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.[55] A correction to the 2019 ARVC risk calculator was proposed,[56] but it may overestimate the risk.[7] 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,[36] and positive [41] results reported. Family history is of rather limited value in predicting SCD.[25] 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.[5, 19] The genotype of ARVC mutation carriers impacts clinical course on the clinical course and disease expression.[24] Desmosomal mutations, particularly for plakophilin(*PKP2*), are an important risk factor for ventricular arrhythmic events.[57] Pathogenic desmoplakin (*DSP*) gene variants are associated with a high risk for sustained ventricular arrhythmia.[58] 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).[59]

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.[23] ***Amiodarone*** has been shown to prevent ventricular arrhythmias more effectively than beta blockers in ARVC patients treated with ICD.[60] ***Sotalol*** at high doses (320-480 mg daily) has also been found partially effective,[61] and ***beta blockers*** should, theoretically at least, be efficacious (Table 8). [40] 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.[62] Treatment with ***ICD*** is indicated in patients with cardiac arrest, syncope, or haemodynamically poorly-tolerated VT, or one or more risk factors for SCD. Specific recommendations for ARVC are provided in Table 8 and Figure 9, and foe ACM, in general, in Figures 10-13. 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).[4]

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.[53] 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,[40] 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.[28]

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.[1, 63-66]

Pregnancy

It is well tolerated in patients with ARVC 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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