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REVIEW

Arrhythmogenic ventricular cardiomyopathy: A paradigm shift from right to biventricular disease

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Abstract

Arrhythmogenic ventricular cardiomyopathy (AVC) is generally referred to as arrhythmogenic right ventricular (RV) cardiomyopathy/dysplasia and constitutes an inherited cardiomyopathy. Affected patients may succumb to sudden cardiac death (SCD), ventricular tachyarrhythmias (VTA) and heart failure. Genetic studies have identified causative mutations in genes encoding proteins of the intercalated disk that lead to reduced myocardial electro-mechanical stability. The term arrhythmogenic RV cardiomyopathy is somewhat misleading as biventricular involvement or isolated left ventricular (LV) involvement may be present and thus a broader term such as AVC should be preferred. The diagnosis is established on a point score basis according to the revised 2010 task force criteria utilizing imaging modalities, demonstrating fibrous replacement through biopsy, electrocardiographic abnormalities, ventricular arrhythmias and a positive family history including identification of genetic mutations. Although several risk factors for SCD such as previous cardiac arrest, syncope, documented VTA, severe RV/LV dysfunction and young age at manifestation have been identified, risk stratification still needs improvement, especially in asymptomatic family members. Particularly, the role of genetic testing and environmental factors has to be further elucidated. Therapeutic interventions include restriction from physical exercise, beta-blockers, sotalol, amiodarone, implantable cardioverter-defibrillators and catheter ablation. Life-long follow-up is warranted in symptomatic patients, but also asymptomatic carriers of pathogenic mutations.

Key words: Arrhythmogenic right ventricular dysplasia/cardiomyopathy; Arrhythmias; Ventricular tachycardia; Sudden cardiac death; Implantable cardioverter defibrillator

Core tip: This manuscript constitutes an updated overview about arrhythmogenic ventricular cardiomyopathy (AVC) and describes well the paradigm shift in the understanding of AVC from an isolated right-sided entity to biventricular disease that can present with multiple facets. The most recent advances in molecular and clinical research are discussed, with particular focus on genetic novelties and risk stratification. We believe that this review will help clinicians to better understand the pathomechanisms that lead to AVC, its diagnosis and state-of-the-art therapeutic decision making.

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INTRODUCTION

Arrhythmogenic ventricular cardiomyopathy (AVC), as

recently re-named by the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) consensus statement paper[1], is generally referred to as arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), constituting a hereditary cardiomyopathy usually with an autosomal-dominant inheritance pattern. Its first description by Giovanni Maria Lancisi, the Pope's physician, dates back to 1736 in his book "De Motu Cordis et Aneurysmatibus"[2]. The first comprehensive description of ARVC/D by Guy Fontaine in 1978 marks a milestone for our current understanding of this heterogeneous disease[3]. Initially, ARVC/D was thought to be an embryological aberration, such as Uhl's anomaly leading to the original designation of dysplasia[4]. However, further research shed light on the pathophysiology of ongoing genetically determined myocardial atrophy that did not support the theory of a congenital myocardial absence. Thus, in 1995, ARVC/D was assigned to the World Health Organization's definition and classification of primary cardiomyopathies[5]. Autopsy studies have been crucial in understanding AVC. Progressive atrophy of the ventricular musculature due to cumulative myocyte loss and infiltration by fibrous and adipose tissue can be observed.

The right ventricle (RV) is primarily affected in AVC, representing the most common form known as ARVC/D, and thus can be referred to as classic AVC[6]. At a later stage, the left ventricle (LV) can also be involved and is often associated with severe disease and a worse prognosis[7]. Advanced molecular genetic studies have identified causative mutations in genes encoding proteins of the intercalated disk, mainly desmosomal proteins[8] that lead to reduced electrical and mechanical stability of the myocardium[9,10]. Subsequent myocardial inflammation, apoptosis and necrosis may occur. Some of these histological changes are currently discussed as potential cases of myocarditis mimicking AVC[11-14]. Because of the genetic basis and the many facets of the disease, the term "ARVC" is somewhat misleading. Particularly as biventricular involvement and less often isolated LV involvement may be present in a substantial proportion of patients[15], a broader term such as "arrhythmogenic cardiomyopathy" should be preferred, as already suggested by Gallo *et al*[16] almost 20 years ago, and as recently proposed by the HRS and the EHRA[1]. However, the cardiology community is still reluctant to accept the proposed new nomenclature, probably because RV involvement constitutes a hallmark of the disease and non-classic forms are difficult to distinguish from non-ischemic dilated cardiomyopathies.

EPIDEMIOLOGY

In most parts of the world, phenotypic expression is more common in men than in women (2-3:1)[17,18]. AVC commonly manifests during late childhood or adolescence but can also emerge in the elderly[19,20]. With a general prevalence of 1:2000, which can be higher in certain geographical regions with enhanced genetic prevalence such as the Veneto region or the Greek island Naxos, it is not so rare[21,22]. Recent data indicates that the prevalence is even higher than initially estimated[23]. AVC is recognized as a leading cause of sudden cardiac death (SCD) in young adults ≤ 35 years of age and may account for up to 10% of cardiovascular deaths in the < 65 age group[24,25]. Of note, in one series from northern Italy, AVC accounted for up to 22% of SCD in all young adults ≤ 35 years of age[26-29]. AVC usually first manifests with ventricular tachyarrhythmias (VTA) or SCD. In its most common form ARVC/D, ventricular arrhythmias originate in the RV and thus have left bundle branch block (LBBB) morphology[28,30]. Less often, the primary manifestation can be heart failure without symptomatic arrhythmias. As LV function is often preserved at early stages, ventricular tachycardia (VT) may be asymptomatic as far as it does not degenerate into ventricular fibrillation (VF)[29]. An early concealed phase without gross structural abnormalities is unique among the primary cardiomyopathies. On the contrary, in hypertrophic cardiomyopathy, arrhythmic risk can be ascribed to the underlying myocardial disarray. In dilated cardiomyopathy (DCM), arrhythmias generally concur with significant LV systolic dysfunction[31]. Of note, early AVC may resemble myocardial channelopathies, such as Brugada syndrome (Bs)[32], thus making correct diagnosis and risk stratification difficult.

DISEASE SUBTYPES

Classification of AVC into three different subtypes is evolving. AVC in its classic right-dominant form is the most common and best known and referred to as ARVC/D. The non-classic forms were first described by pathologists on autopsy studies and in isolated clinical case reports[33,34]. Through intensive *in vivo* characterization of affected families, a link to hereditary mutations of the intercalated disk was established[35-37]. LV involvement is increasingly described with a prevalence of up to 76% of cases, which may be attributed to improved diagnostic methods such as genetic testing, high-resolution contrast-enhanced cardiac magnetic resonance tomography (CMR), and recently the new technology of echocardiographic strain imaging[38]. The proposed classification below is simplistic since due to genetic heterogeneity and epigenetic factors, a phenotypic continuum with right- and left-dominant subtypes at opposite ends has to be assumed.

In classic right-dominant ARVC, a dilated RV with fibro-fatty infiltration with no or only minimal LV involvement can be found at autopsy (Figure 1). This fibro-fatty infiltration typically begins subepicardially and may expand transmurally over time[39]. Papillary muscles and trabeculae are generally not involved in this process[25]. Yet, fatty infiltration alone does not constitute a pathognomonic sign of AVC, as a certain amount of epicardial and intramyocardial fat without an increase in fibrous tissue is present in both ventricles, more commonly in the RV, of persons without cardiovascular disease, particu-

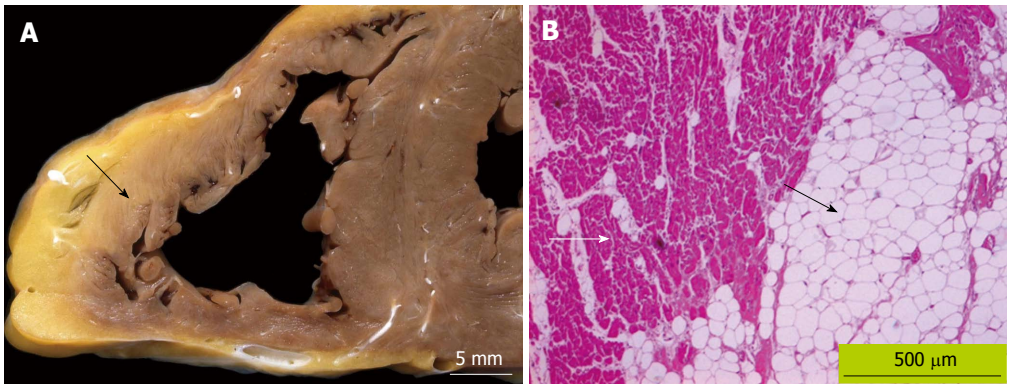

Figure 1 Typical pathology findings in arrhythmogenic ventricular cardiomyopathy/dysplasia. A: Macroscopic finding in a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). The myocardium of the right ventricular free wall is partially replaced by fibro-fatty tissue (black arrow) that typically begins in the epicardial region and at later stages expands transmurally; B: Endomyocardial biopsy from a patient with ARVC/D demonstrating fatty (black arrow) replacement of the right ventricular myocardium. Strands of myocardium are still visible (white arrow, heidenhain trichrome, magnification × 60).

larly in the obese and elderly[17,40,41]. Another consistent finding in AVC is myocardial atrophy. Myocardial wall thinning, but also thickening, can both be seen on macroscopic examination[22,40]. The subtricuspid region and the thin RV outflow tract (RVOT) are particularly prone to ventricular bulging and aneurysm formation that is present in 20%-50% of autopsy cases of ARVC/D[39]. The former concept of early RV apical involvement and the term "triangle of dysplasia" have recently been questioned[42]. Even although not very specific, ventricular aneurysms are strongly associated with the disease. The fact that the interventricular septum is rarely affected by fibro-fatty infiltration is an important disadvantage of endomyocardial biopsies, usually obtained from the septum, which may frequently yield false-negative results[43]. If an affected region can be obtained for histological evaluation, it may reveal both replacement fibrosis, a repair mechanism after myocyte loss, and interstitial fibrosis, a reactive process, *e.g.,* to inflammation[36,39].

Biventricular AVC is characterized by early and parallel involvement of both ventricles that can only be visualized by advanced imaging techniques such as contrast CMR or strain echocardiography[36,44]. Progressive disease is characterized by systolic impairment and biventricular dilation with clinical features of global congestive heart failure. In contrast to other cardiomyopathies with biventricular involvement, ventricular arrhythmias of both right bundle branch block (RBBB) and LBBB configuration are present at an early stage, with around 10% of patients presenting with both[31].

Left-dominant AVC (ALVC) has recently been suggested as a distinct form of AVC and is characterized by the early occurrence of LV involvement, while global RV function is preserved[36]. An overlap with idiopathic myocardial fibrosis (IMF) accounting for certain SCD cases in a post mortem series has been reported[45]. Typically, IMF features diffuse interstitial and replacement fibrosis with a predilection for the inferior LV wall in the absence of coronary artery disease and other structural abnormalities. Of note, myocardial infiltration by adipocytes is lacking in IMF. In biventricular disease or ALVC, ventricular arrhythmias may also originate from the LV and thus show a RBBB configuration. Structural and electrocardiographic (ECG) findings are the left-sided analogues to those observed in ARVC/D (Table 1). The RV to LV ratio typically remains < 1.0. To better understand ALVC and its clinical course, future investigations will be required.

PATHOGENESIS

Genetically-determined disruption of intercalated-disk integrity is a key factor promoting the development of AVC and SCD. This is widely named the "defective desmosome" hypothesis[46,47]. Recent data indicates that loss of desmosomal integrity can substantially affect gap junctions, sodium channel function and electrical propagation at the micro- and nano-scale, thereby promoting ventricular arrhythmias in the absence of overt structural damage[48]. Accordingly, lethal arrhythmias such as VF and polymorphic VT often occur during these concealed early stages, while sustained monomorphic VT occur at later stages, where there is enough substrate for macro-re-entry. Delmar *et al*[9] thus have postulated that mutations in desmosomal genes may affect the integrity of other molecular complexes that reside in proximity to desmosomes, such as connexins and voltage gated sodium channels, and are crucial for electrical synchrony. This molecular complex and its interactions have been named the cardiac connexome[49,50]. Yet, genetic mutations in gap junctions such as connexin-43 have not been associated with AVC so far[10,51].

Currently, two theories for the understanding of progressive fibro-fatty replacement of the myocardium exist: (1) inflammation as a response to myocardial injury[4,25,39]. Lymphocytic interstitial infiltrates surrounding foci of necrotic or degenerative myocytes are observed on histopathology. Myocyte cell death may occur *via* apoptosis or necrosis underlying chronic inflammation. Acute myocyte cell death has also been reported, suggesting acute myocarditis during the disease course[52]. Periodic exacerbations of a previously quiescent disease may be

Table 1 Characteristics of arrhythmogenic ventricular cardiomyopathy

	Classic right dominant form (ARVC/D)	Left dominant form
12-lead surface ECG	Intraventricular conduction delay in V1-V3	Leftward QRS axis (< 0°)
	QRS complex prolongation V1-V3	ε like waves in inferior or lateral leads
	ε wave in V1-V3	LBBB
	(Incomplete) RBBB	Inverted T-waves in infero-lateral leads
	Inverted T-waves in V1-V3	Inverted T-waves V1-6 with biventricular involvement
	Inverted T-waves in V1-V6 with biventricular involvement	-
	ST elevation in V1-V3	-
	Poor R wave progression	
Signal-averaged ECG	Late potentials	-
Arrhythmia	PVC/VT of LBBB configuration	PVC/VT of RBBB configuration
Ventricular volumes	Mild to severe RV-dilation ± dysfunction	Mild to severe LV-dilation ± dysfunction
RV/LV volume ratio	⩾ 1.2, increases with disease expression	< 1.0
Other imaging abnormalities	Regional wall motion abnormalities in RV	Regional wall motion abnormalities in LV
	RV aneurysms	Non-compacted appearance
	Fat/LGE in RV myocardium	LGE in the subepicardial and midwall LV myocardium
Genetics	Affected genes currently known to be associated with AVC	Association with TMEM43 and phospholamban mutations[1]

Adapted from Jacoby *et al*[84]. ARVC/D: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; ECG: Electrocardiogram; ε: Epsilon; LBBB: Left bundle branch block; LGE: Late gadolinium enhancement; LV: Left ventricle; PVC: Premature ventricular contraction; RBBB: Right bundle branch block; RV: Right ventricle; VT: Ventricular tachycardia; AVC: Arrhythmogenic ventricular cardiomyopathy; TMEM43: Transmembrane protein 43.

triggered by such inflammatory episodes and are called "hot phases" of AVC. Occasionally, these phases may clinically present with chest pain, dynamic ECG changes and increased arrhythmic activity[31]. Strenuous physical activity can trigger inflammation as mechanical stress to the impaired intercalated disk leads to myocyte detachment and myocyte cell death[53]. It is important to keep in mind that isolated myocarditis, sarcoidosis, Bs and other diseases can mimic AVC[14], which may prompt further histological and molecular investigations. If molecular genetic analyses or pedigree analyses of affected family members are not performed, a biopsy specimen may be classified as focal myocarditis[36]. Yet, previous studies have indicated a link between AVC and a susceptibility to viral and bacterial myocarditis, particularly in non-hereditary forms[54,55]. The prevalence of viral genome in myocardial biopsies from AVC patients is reported with a broad range from 0% to 75%, but a causal association is difficult to prove. Presence of enteroviral RNA has been reported in tissue from patients with DCM, suggesting an innocent bystander role. Nevertheless, viral presence may play a secondary yet important role in disease progression[47]; and (2) apoptosis following disruption of the intercalated disc[56] with electromechanical instability, as indicated by detection of fragmented DNA, expression of protease CPP-32 by immunohistochemistry and positive Tc-annexin V scintigraphy *in vivo*[11-14,57,58]. These histological disarrangements create a substrate for electrical re-entrant phenomena and delayed ventricular activation triggering ventricular arrhythmias. Of note, as AVC can cause ventricular arrhythmias and SCD in the absence of gross macroscopic abnormalities, histological and molecular examinations are important to establish a post-mortem diagnosis[59]. Other investigators observed that epicardium-derived cell cultures obtained from neonatal hearts lacking plakophilin-2 (PKP2), an important desmosomal gene, revealed enhanced cell migration velocity and proliferation, leading to the hypothesis that desmosomal mutations may cause infiltration of fibroblasts and adipocytes from the epicardial cell layer into the myocardium[60]. This hypothesis is consistent with the frequent clinical observation that fibro-fatty infiltration progresses from the epicardium towards the endocardium.

GENETICS

Analyses of the first- and second-degree relatives of patients suggest that up to 50% of AVC cases are familial[61,62]. AVC is most commonly inherited as a Mendelian autosomal dominant trait with incomplete penetrance[46,47], although two autosomal recessive forms have been described[63-65]. To date, 12 different AVC loci are reported in the Online Mendelian Inheritance in Man (Table 2)[66]. Compound and digenic heterozygosity has been recently suggested, indicating that in some cases more than one pathogenic allele may be involved in the disease process[65,67,68]. As penetrance is incomplete, genetically affected relatives often demonstrate variable and mild phenotype and the prevalence of familial disease is often underestimated in clinical practice[31,62]. The fact that AVC can be inherited has been known since 1982 after the description of 24 adult cases, two in the same family, by Marcus *et al*[69]. Six years later, the autosomal dominant pattern of inheritance with incomplete penetrance and variable expression was demonstrated in a study of nine Italian families[26]. As patients with fully penetrant cardiomyopathy and readily discernible features of the palms, plantar fascia and hair were clustered in families on the Greek island Naxos, an autosomal recessive mutation in the desmosomal protein junction plakoglobin (JUP) was finally discovered, which became known as Naxos disease. Myocytes and epidermal cells share similar intercalated disks (desmosomes and fascia adherens) and are both exposed to high shear stress, the

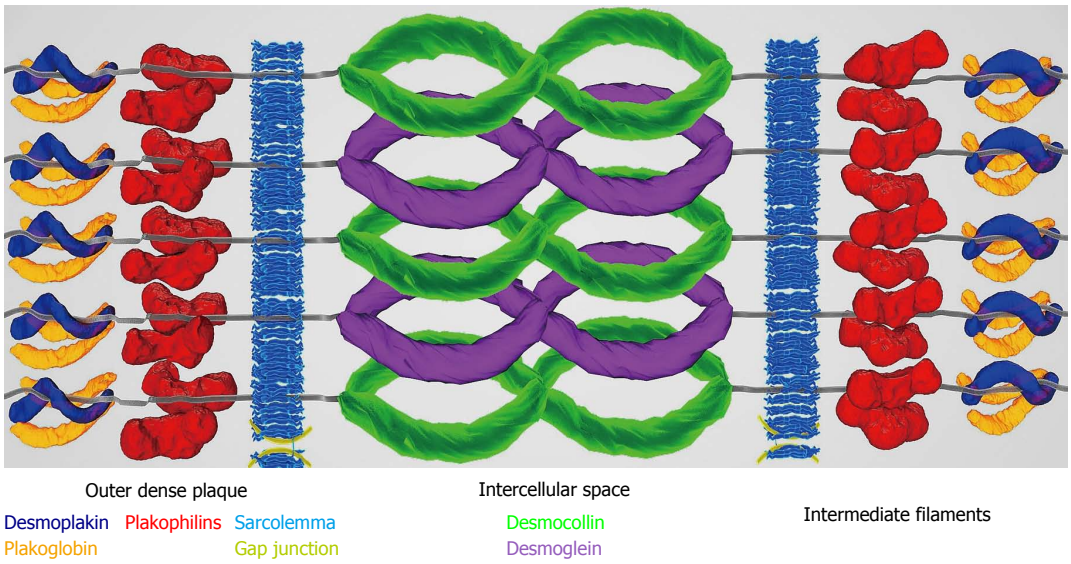

Figure 2 Molecular model of the desmosome: in the desmosomal complex the intermediate filaments of the cytoskeleton (desmin in the heart) are linked to the transmembranous cadherins (desmocollin and desmoglein) *via* armadillo proteins (plakoglobin and plakophilin) and desmoplakin. This interaction is crucial for myocardial mechanical and electrical stability. Mutations in arrhythmogenic right ventricular cardiomyopathy mostly affect desmosomal proteins.

Table 2 Arrhythmogenic ventricular cardiomyopathy classification, from OMIMTM Online Mendelian inheritance in Man

AVC subtype	Chromosome/locus	Mode of transmission	Encoded protein
ARVC/D 1	14q23-q24	Autosomal-dominant	TGFβ3
ARVC/D 2	1q42-q43	Autosomal-dominant	RyR2
ARVC/D 3	14q12-q22	Autosomal-dominant	-
ARVC/D 4	2q32	Autosomal-dominant	TTN
ARVC/D 5	3p23	Autosomal-dominant	TMEM43
ARVC/D 6	10p12-p14	Autosomal-dominant	-
ARVC/D 7	10q22	Autosomal-dominant	-
ARVC/D 8	6p24	Autosomal-dominant	DSP
ARVC/D 9	12p11	Autosomal-dominant	PKP2
ARVC/D 10	18q12	Autosomal-dominant	DSG2
ARVC/D 11	18q12.1	Autosomal-dominant	DSC2
ARVC/D 12	17q21	Autosomal-dominant	JUP
Naxos disease	17q21	Autosomal-recessive	JUP

AVC: Arrhythmogenic ventricular cardiomyopathy; ARVC/D: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; TGF: Transforming growth factor; RyR2: Ryanodine receptor 2; TTN: Titin; TMEM43: Transmembrane protein 43; DSP: Desmoplakin; PKP2: Plakophilin-2; DSG2: Desmoglein-2; DSC2: Desmocollin-2; JUP: Junction plakoglobin.

heart particularly during strenuous physical activity and increased cardiac workload. Thus, it has been assumed that common genes encoding proteins of the intercalated disk might be responsible for AVC. In 1994, the first chromosomal locus (14q23-q24) for autosomal dominant AVC was reported in Italy[47]. Linkage analyses shed light on its genetic heterogeneity with sequential discovery of several loci on chromosomes 1, 2, 3, 6, 10, 12, 14, 17 and 18 (Table 2). Most frequently, mutations in genes encoding components of the cardiac desmosome, an important protein complex of the intercalated disk (Figure 2), are associated with AVC, resulting in impaired intercalated-disk integrity[62,67,68]. The pathogenic importance of desmosomal mutations was confirmed by electron microscopy and immunohistochemistry[2,56]. Intercellular junctions consist of a core region that mediates cell-cell adhesion and a plaque region that provides attachment to the intermediate filaments within the myocyte. Three groups of desmosomal proteins are known: (1) transmembrane desmosomal cadherins including desmocollins 2 and desmogleins 2 (DSG2); (2) desmoplakin (DSP), a plakin family protein that attaches directly to intermediate filaments (desmin in the myocardium); and (3) linker proteins such as armadillo family proteins including JUP (catenin-γ) and PKP2 that mediate interactions between the desmosomal cadherin tails and DSP[70]. In about 80% of cases with confirmed pathogenic mutations, PKP2, DSP and DSG2 are altered[22]. Besides desmosomal gene mutations, mutations in genes encoding proteins that interact with desmosomal proteins were found as well. These include: (1) the transforming growth factor β3 that conveys cytokine-stimulating fibrosis and modulates cell adhesion and growth[52]; (2) the human ryanodine receptor 2 (RyR2) that induces the release of calcium from the myocardial sarcoplasmic reticulum and that is also associated with catecholaminergic polymorphic VT (CPVT)[71]; (3) the transmembrane protein 43 (TMEM43) discovered in the Canadian Newfoundland founder population and Europe[72] that functions as a PPAR-γ response element, an adipogenic transcription factor; (4) the intermediate filament desmin; (5) the tumor protein 63; and (6) recently, titin (TTN) that bridges the sarcomere along its longitudinal axis and forms a continuous filament along the myofibril[66]. As TTN binds to the transitional junction of the intercalated disk, this may explain a functional link to the desmosome[66,73,74]. Current molecular studies are screening other components of the desmosome and related proteins, such as plectin and pinin (Table 3)[75]. NFκB interacting protein-1 is another extra-desmosomal gene of interest, which has been isolated in Poll-Here-

Table 3 Future candidate proteins for arrhythmogenic ventricular cardiomyopathy

Encoded protein
Components of the desmosome
Plectin
Emerin
Components of the adherens junction
β-catenin
α-catenin
N-cadherin
Components of the gap junction
Connexin 43
Myotonic dystrophy protein kinase-1
Laminin receptor-1
Components of dystrophin-glycoprotein complex

ford cattle with recessive AVC and woolly hair coat syndrome[76]. Yet, the pathogenic role of NFκB interacting protein-1 mutations in humans has to be demonstrated in future studies.

MODIFIER GENES AND ENVIRONMENTAL FACTORS

Although a plethora of pathogenic mutations exists, these mutations cannot account for the entire broad spectrum of disease expression. Data from the Newfoundland founder population and populations from the Dutch and Swiss ARVC/D registries show a strong male predominance of disease expression[77]. A modifier effect of testosterone has been discussed. Yet, this male predominance has not been confirmed in the Johns Hopkins ARVC/D cohort, which may be associated with similar exercise levels among males and females in the United States. Nevertheless, outcomes were strongly gender dependent in all of those cohorts, with male gender constituting an independent risk factor for adverse outcomes[37,62,72,78,79]. In one study, 67% of family members showed discordant disease patterns between RV and LV involvement[31]. Recent data pointing at the importance of compound and digenic heterozygosity indicates that modifier genes may account for residual variation and disease severity[68,80]. The first evidence for environmental influences in AVC arose from monozygotic twin studies, where differences were reported in symptom onset, structural severity and arrhythmic risk. Strenuous physical activity seemed to play an important role in these four cases[81]. These preliminary observations were confirmed in two recent studies, in which endurance training and frequent exercise were associated with earlier disease manifestation and disease severity[31,82]. Future studies will be crucial to distinguish between pathogenic mutations and innocent bystander mutations and to define the role of epigenetic factors in disease manifestation and progression. As recently proposed by the HRS/EHRA consensus statement, genetic testing should only be performed if the signal-to-noise ratio is expected to be > 10[1].

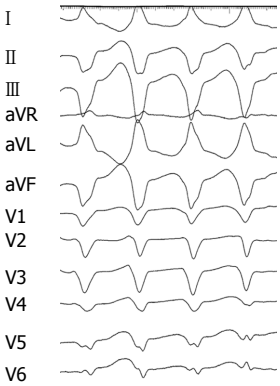

Figure 3 Monomorphic sustained ventricular tachycardia with left bundle branch block morphology and superior axis (Ⅱ, Ⅲ, aVF negative), a major criterion for arrhythmogenic right ventricular cardiomyopathy/dysplasia according to the revised 2010 task force criteria.

CLINICAL PRESENTATION

AVC has a reported community-based prevalence of 1 in 2000 and thus cannot be classified as a "rare" disease according to the 2007 European definition. These numbers reflect the importance of appropriate diagnostic tools as it is often underdiagnosed, particularly in early and mild cases. The above mentioned non-classic subtypes are usually not considered or misattributed as DCM. Some forms mimic myocarditis. Early disease with arrhythmias but without overt structural changes may be misjudged as idiopathic VT or ventricular ectopy[36,46]. In the elderly, AVC is rarely considered as a differential diagnosis, which is certainly a false assumption. All these aspects infer that real-world prevalence is higher. In the following section, we provide an overview of clinical symptoms and signs that shall increase awareness of the disease, particularly in non-classic forms, for timely diagnosis and prevention of SCD. AVC should be suspected if the following symptoms or signs occur: (1) palpitations; (2) presumably arrhythmic presyncope or syncope; (3) VT with LBBB morphology; (4) aborted SCD. Palpitations and (pre)syncope are the most frequent symptoms[17]. A high clinical suspicion should be raised if these symptoms correlate with premature ventricular contractions (PVC) or VT with LBBB morphology, particularly with a superior axis (Figure 3). However, ALVC or biventricular disease can present with VT with RBBB morphology or both (Table 1, Figure 3). The presence of monomorphic VT is associated with late disease stages, although gross structural changes are not mandatory[28,83]. Recently, disease severity, VT frequency and early onset of VT have been associated with the presence of common desmosomal mutations, particularly if more than one pathogenic variant was present[62,67,84]. Up to 25% of patients present with supraventricular tachycardia (SVT), most frequently atrial fibrillation, which is associated with male gender, increasing age and left atrial enlargement in AVC[85]. SVT are very important as they are associated with inappropriate implantable cardioverter defibrillator (ICD) shocks

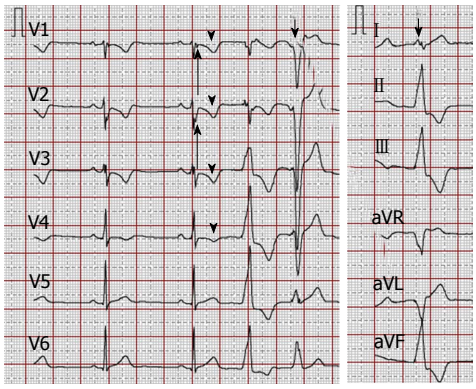

Figure 4 Electrocardiographic findings. A 12-lead surface electrocardiogram (25 mm/s, 10 mm/mV) showing typical depolarization abnormalities (prolonged terminal activation duration in V1-V2, a minor criterion according to 2010 task force criteria, long arrows) and repolarization abnormalities (T-wave inversions V1-V4 in the absence of complete right bundle branch block, a major criterion according to 2010 task force criteria, arrowheads), and premature ventricular contractions with two different morphologies (short arrows).

and an increased risk of both heart failure and death. Furthermore, atrial arrhythmias present at a younger age than in the general population[86]. It is not rare that AVC first manifests as SCD, with some authors reporting an annual incidence of 9%[87]. Whereas some authors report that SCD occurs preferentially during strenuous physical activity[25,87,88], according to others it may often occur in the sedentary state[13,25]. In ARVC/D caused by TMEM43 mutations, enhanced sympathetic activity as a trigger for lethal arrhythmias is established[71]; (5) chest pain with or without dynamic ST elevation/T-wave changes on 12-lead surface ECG ± rise in cardiac biomarkers; and (6) presumed DCM with early onset and frequent ventricular arrhythmias. Precordial T-wave inversions beyond V1 after puberty (Table 1, Figure 4) and T-wave inversions in the right precordial leads V1-V3 may potentially be benign, particularly before puberty. Their prevalence among athletes and sedentary controls is similar[89], suggesting that this is not a training-related phenomenon. According to recent recommendations, a further evaluation with transthoracic echocardiography (TTE) may be performed after puberty. If imaging is inconclusive, regular follow-up by serial clinical examinations, ECG and TTE can be performed as structural alteration may become apparent after several years[90,91]. RV failure with dyspnea and signs of right sided heart failure are rather rare and reported in up to 6% of patients at initial presentation. If the LV is involved, congestive heart failure may occur. Importantly, the clinician should be aware that AVC cannot be excluded by the absence of structural abnormalities as arrhythmias often occur in the "concealed phase" and structural abnormalities may follow after years. In a review reporting 37 families with AVC index patients, only 151 of 365 family members had clinically manifested disease and 17 family members were healthy despite a pathogenic mutation[28]. Thus, genetic screening of family members may help to identify AVC, although a negative test does not exclude it.

DIAGNOSIS

Revised 2010 task force criteria

Currently, no gold standard to establish or exclude the diagnosis of AVC exists. In 2010, the original 1994 task force criteria (TFC) for diagnosis of ARVC/D by Marcus *et al*[92] were revised in order to enhance diagnostic sensitivity and particularly to improve identification of affected asymptomatic family members[93]. The importance of pathogenic mutations was acknowledged and precise cut-off values for imaging and histological evaluation were provided. The impact of these changes is currently being evaluated. Some investigators report an increased diagnostic yield with the revised TFC[94,95], while others could not demonstrate a benefit[96,97]. It is important to keep in mind that these TFC only apply to ARVC/D with or without LV involvement. The revised TFC assign the findings into six categories (Table 4): (1) global and/or regional myocardial dysfunction and structural abnormalities; (2) histological characterization; (3) repolarization abnormalities on 12-lead surface ECG; (4) depolarization abnormalities on 12-lead surface ECG; (5) arrhythmias; and (6) family history and genetics.

Definite diagnosis requires 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria from different categories. ARVC/D is considered "borderline" if 1 major and 1 minor criterion, or 3 minor criteria are present. ARVC/D is still "possible" if 1 major criterion or 2 minor criteria are present. For each individual, comprehensive non-invasive evaluation is necessary. This includes a thorough clinical history and examination, pedigree analysis, 12-lead surface ECG, TTE with detailed assessment of the RV, CMR, stress testing in order to induce arrhythmias, and Holter ECG monitoring. If suspicion remains high and symptoms are rare, event recorders and invasive procedures may be needed.

Physical examination

Fifty percent of patients will have a normal physical exam. The other 50% will show abnormalities such as giant a-waves on the jugular veins, tricuspid regurgitation murmur, a fixed splitting of S2, and right-sided S3-S4 at the left sternal border with augmentation during inspiration in case of RV dilation[88,98].

12-lead surface ECG and signal-averaged ECG

An abnormal 12-lead surface ECG will be present in about 50% of patients with ARVC/D. In one study, ECG was abnormal in 90% of patients after a follow-up period of 6 years[99]. Abnormalities include epsilon waves, a QRS duration ⩾ 110 ms in V1-V3, and T-wave inversions in the right precordial leads (Figure 4). A prolonged terminal activation duration (measured from the nadir of the S wave until the end of the QRS complex) in V1-V3 ⩾ 55 ms is considered as a minor criterion for ARVC/D and has been reported as the first sign in young asymptomatic family members[45,62,100]. However, interpretation of ECG findings, apart from T-wave inversions, significantly var-

Table 4 Revised (2010) task force criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia, adapted from Marcus *et al*[92]

	Structural alterations
Major	TTE regional RV akinesia, dyskinesia, or aneurysm and 1 of the following criteria (end diastole)
	PLAX RVOT ≥ 32 mm [(PLAX/BSA) ≥ 19 mm/m^2]
	PSAX RVOT ≥ 36 mm [(PSAX/BSA) ≥ 21 mm/m^2]
	Or RV fractional area change ≤ 33%
	CMR regional RV akinesia, dyskinesia, or dyssynchronous RV contraction and 1 of the following criteria (end diastole)
	RV end-diastolic volume/BSA ≥ 110 mL/m^2 (♂) or ≥ 100 mL/m^2 (♀)
	Or RV ejection fraction ≤ 40%
	RV angiography regional RV akinesia, dyskinesia, or aneurysm
Minor	TTE regional RV akinesia, or dyskinesia and 1 of the following criteria (end diastole)
	PLAX RVOT ≥ 29-31mm [(PLAX/BSA) ≥ 16-18 mm/m^2]
	PSAX RVOT ≥ 32-35 mm [(PSAX/BSA) ≥ 18-20 mm/m^2]
	RV fractional area change > 33%-39%
	CMR regional RV akinesia, dyskinesia, or dyssynchronous RV contraction and 1 of the following criteria (end diastolic)
	RV end-diastolic volume/BSA ≥ 100-109 mL/m^2 (♂) or ≥ 90-99 mL/m^2 (♀)
	Or RV ejection fraction > 40%-44%
	Histopathology (endomyocardial biopsy)
Major	Residual myocytes < 60% by morphometric analysis with fibrous replacement of the RV free wall myocardium ≥ 1 sample, with or without fatty replacement
Minor	Residual myocytes 60%-75% by morphometric analysis with fibrous
	Replacement of the RV free wall ≥ 1 sample
	Repolarization abnormalities (> 14 years of age)
Major	T-wave inversions V1-V3 or beyond (in absence of complete RBBB)
Minor	T-wave inversions V1-V2 or V4-V6 (in absence of complete RBBB)
	T-wave inversions V1-V4, if complete RBBB present
	Depolarization abnormalities
Major	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T-wave) in V1 to V3
Minor	SAECG with late potentials (if QRS complex on standard surface ECG < 110 ms) or terminal activation duration of QRS ≥ 55 ms in V1, V2 or V3
	Arrhythmias
Major	VT of LBBB morphology with superior axis
Minor	VT of RVOT configuration, LBBB morphology with inferior axis or of unknown axis
	> 500 PVC per 24 h (holter)
	Family history
Major	ARVC/D in a first-degree relative who meets current TFC
	ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
	Identification of a pathogenic mutation categorized associated with ARVC/D in an index patient
Minor	Suspected ARVC/D in a first-degree relative-premature SCD (< 35 years of age) due to suspected ARVC/D in a first-degree relative
	ARVC/D confirmed pathologically or by current TFC in second-degree relatives

Definite diagnosis: two major or one major and two minor criteria or four minor from different categories; Borderline diagnosis: one major and one minor or three minor criteria from different categories; Possible diagnosis: one major or two minor criteria from different categories. BSA: Body surface area; CMR: Cardiac magnetic resonance tomography; LV: Left ventricle; PLAX: Parasternal long-axis view; PSAX: Parasternal short-axis view; RBBB: Right bundle branch block; RVOT: Right ventricular outflow tract; RV: Right ventricle, TTE: Transthoracic echocardiogram, PVC: Premature ventricular contraction VT: Ventricular tachycardia; SAECG: Signal-averaged electrocardiographic; LBBB: Left bundle branch block; ARVC/D: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; TFC: Task force criteria; SCD: Sudden cardiac death.

ies among observers (unpublished data as yet from our group). This is particularly true for what is considered an epsilon wave. A limitation of T-wave inversions is the fact that they can also be found in healthy individuals, patients with anterior ischemia or RV hypertrophy[90,101]. A recent study highlighted the importance of serial ECG evaluations as dynamic ECG changes occurred in 23% of patients over a median follow-up period of 34 mo, but these were not paralleled by structural abnormalities[102]. Fibro-fatty infiltrations disrupt the electrical continuity of myocardial fibers. This leads to fragmentation and delay of ventricular depolarization (zig-zag pathways). On the surface, this may be visible as QRS fragmentation[103], late ventricular potentials of small amplitude such as epsilon waves[104], or late potentials recorded by signal-averaged ECG (SAECG)[87,105]. An abnormal SAECG (a minor criterion) indicates progressive disease and may predict VT, although a recent study has questioned the latter[28,106]. SAECG may not be sensitive enough to detect early forms of AVC[28].

Stress testing

Exercise can induce ventricular arrhythmias and is important in patients with suspected AVC. However, VT with LBBB morphology and inferior axis can occur in both ARVC/D and idiopathic RVOT-VT without underlying structural abnormalities[107]. A recent study has proposed ECG criteria and a scoring system to distinguish between the two entities[108].

Transthoracic echocardiography

In many centers, TTE constitutes the initial imaging tool for evaluation of patients with suspected AVC and for screening family members as it is readily available and

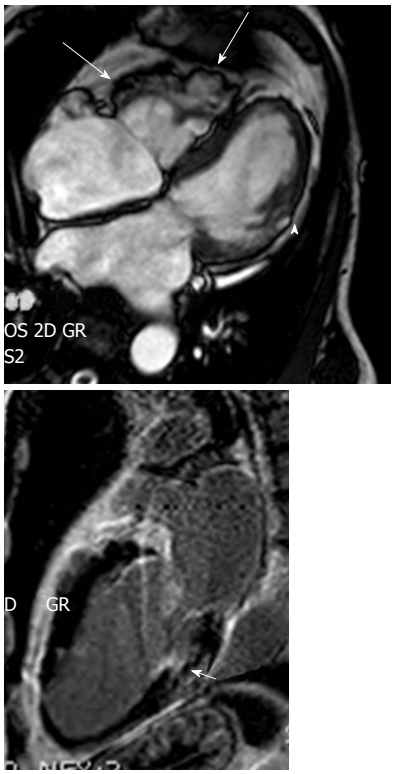

Figure 5 Regional right ventricular dyskinesia of the right free wall detected by cardiac imaging are considered as a major criterion for right ventricular cardiomyopathy/dysplasia according to the revised task force criteria if additionally right ventricle dilation or impaired right ventricle ejection fraction are present. These cardiac magnetic resonance images (upper panel 4-chamber view, lower panel 2-chamber view late sequences) show aneurysms of the RV free wall (long arrows), and LV involvement detected by a small akinetic region (arrowhead) and late gadolinium enhancement of the posterior LV wall (short arrow), confirming biventricular involvement. ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia; RV: Right ventricle; LV: Left ventricle.

rapidly informative. It may demonstrate RV enlargement or multiple areas of dilation and regional contraction abnormalities, mainly in the subtricuspid region, RVOT and RV apex[109]. According to the revised TFC, evaluation and measurements of the RVOT are crucial for diagnosis[110]. The LV can also be affected, particularly in non-classic forms displaying hypokinesia and a reduced ejection fraction, although in most cases LV structural abnormalities are localized in the posterolateral region[111,112].

CMR

CMR has emerged as the non-invasive diagnostic tool of choice for assessing the RV over the past 15 years[45,113]. Besides highly accurate assessment of right sided volumes, myocardial mass and systolic and diastolic function, the contrast-enhanced CMR can reveal intramyocardial fibrosis by late gadolinium enhancement (LGE)[114]. Yet, intramyocardial fat and fibrosis as diagnostic targets in AVC were not integrated in the revised TFC because of the limited specificity of these findings, particularly in the absence of regional wall motion abnormalities, significant intra- and inter-observer variability, and the need for highly specialized interpreters in visualizing the RV myocardium[45,115,116]. In fact, it can be challenging to be certain of LGE within the RV myocardium because of the thin RV and possible confusion with fat. The main difference in CMR criteria compared to the 1994 criteria constitutes the quantification of RV dilation and RV function. CMR plays an important role in diagnosing AVC (Figure 5) but consensus guidelines for non-classic forms are eagerly awaited. Some authors emphasize the importance of combining TTE with CMR to increase diagnostic yield. New diagnostic tools for detection of early diastolic and systolic abnormalities such as three-dimensional echocardiography, strain echocardiography and CMR tagging could facilitate early diagnosis of ACV[117-120]. The promising results of these preliminary studies[121,122] will have to be validated in large prospective studies.

RV angiography

RV angiography is considered a very useful test to diagnose classic forms of AVC and to evaluate RV function[123,124]. Its positive predictive value is above 85%, with a negative predictive value of 95%[88]. Technical aspects of the procedure can be found at *arvd.org*. Good quality images allow global and regional analyses of morphology and wall motion. RV angiography also has certain limitations that explain why it is not widely used in clinical practice. Clinicians want to offer non-invasive strategies without ionising radiation, particularly if patients are young. Additionally, serial follow-up RV angiographies for monitoring disease progression are difficult to perform. It is important to remember that according to the revised 2010 TFC, with all three imaging techniques, hypokinesia is no longer considered diagnostic.

Electrophysiological study and electroanatomical voltage mapping

Arrhythmias can be induced during an electrophysiological study (EPS) with programmed ventricular stimulation. Induction of clinical VT can guide ablation. The susceptibility for arrhythmias, arrhythmia detection, ICD treatment algorithms and efficacy of antiarrhythmic drugs can be assessed. Electroanatomical voltage mapping (EAM) is a technique using electrophysiological catheters to measure local myocardial voltages. After obtaining several hundred points, a voltage map can be reconstructed. According to several studies, healthy RV myocardium displays bipolar voltages > 1.5 mV[125-127]. In myocardium infiltrated by fibro-fatty tissue, abnormally low voltages with a longer duration, splitting and fractionation of signals can be found. Myocardial voltage maps are usually obtained from the endocardium but epicardial measurements after puncturing the pericardial sac are also feasible. EAM has been shown to be safe and to improve outcomes of VT ablation in ARVC/D[128-131]. The diagnostic and prognostic utility of EAM has not yet been implemented in the current TFC. Larger prospective studies may consolidate the role of EAM in the diagnostic armamentarium[125,132,133].

Endomyocardial biopsy

Endomyocardial biopsy (EMB) was considered the di-

agnostic gold standard for AVC for a long time. It may allow confirmation of AVC in an index patient and exclude potential differential diagnoses such as sarcoidosis or Chagas disease. However, EMB are commonly taken from the thicker RV septum to assure a safe procedure. It was recognized that the septum is often spared by fibro-fatty infiltration and thus often yields false-negative results[132,134]. Nevertheless, septal EMB can identify other conditions such as sarcoidosis, myocarditis and IMF. EMB from diseased regions is problematic as these regions are often difficult to reach, very thin and sample acquisition carries an increased risk of perforation and tamponade[4]. Histological analysis should best be performed by an expert cardiac pathologist who judges the amount of surviving myocytes and fibro-fatty replacement. The results can be allocated as one major or one minor criterion according to the revised TFC. As AVC is patchy, several biopsies should be obtained. EAM-guided biopsies taken from low-voltage areas may improve diagnostic yield and better distinguish between myocarditis or sarcoidosis[14,125,135]. Serious concerns remain about the hazards of sampling thin areas, although complication rates in preliminary studies were low[14]. Moreover, EAM-guided EMB may be of limited value in early stages of AVC when serious arrhythmias occur in the absence of gross structural abnormalities. Additional immunohistochemical staining of the intercalated disk, *e.g.*, with plakoglobin, may turn into a valuable tool for pathologists in the future but results very much depend on the protocols used[2]. Confirmation of typical histological changes by cardiac surgery or necropsy can help to confirm the diagnosis and exclude differential diagnoses.

Genetic testing

A consensus statement from the HRS and the EHRA regarding genetic testing in AVC was published recently[1]. The major purposes of genetic testing are to confirm AVC in probands with a high (Class Ⅱa recommendation, level of evidence C) or intermediate (at least 1 major or 2 minor criteria; Class Ⅱb recommendation, level of evidence C) clinical suspicion and to identify genetically-affected relatives harboring the pathogenic mutation (Class I recommendation, level of evidence C), particularly those without overt disease. Genetic testing in probands fulfilling only one minor criterion is not recommended. A family background and identification of a pathogenic mutation has been demonstrated in up to 50%, while in the remaining probands, an underlying familial disease with incomplete penetrance cannot be excluded. The most common mutations are found in PKP2 (80% of mutations in the Dutch and Northern American cohorts) and DSP (39% in the Italian cohort)[80], followed by DSG2[8,47,62,136,137]. It should be kept in mind that molecular genetic testing may only support a clinical diagnosis or suspicion. A negative test does not rule out AVC, because other causal genetic mutations and unknown environmental factors may also cause the disease[47,138]. Pathogenic mutations do not make a diagnosis of AVC itself, as multiple sources of diagnostic information such as ECG changes, ventricular arrhythmias and ventricular abnormalities have to be considered[56]. Yet, the identification of pathogenic mutations may be useful in the differential diagnosis of AVC and phenocopies, such as myocarditis, idiopathic RVOT tachycardia, DCM, muscular dystrophies, IMF or sarcoidosis[35]. Cascade genetic screening of relatives may offer another strategy to serial non-invasive cardiovascular evaluation of family members. Current guidelines[1,87] do not recommend genetic testing for risk stratification and therapeutic decision making in AVC because study results regarding the ability of genotyping to detect malignant mutations associated with an increased susceptibility to potentially lethal arrhythmias have been conflicting[8,62,64,90,139]. Recent large scale studies[8,62] indicate an association between positive mutation carrier status and early disease onset. Thus, genotyping of younger family members should strongly be encouraged. This might be particularly important for patients carrying digenic or compound heterozygote mutations that are reported in up to 18% of the AVC population studied and have been associated with a stronger phenotype[1]. Issues such as the availability of genetic counselling in a multidisciplinary setting[140], low-probability mutations[136], genetic testing for "low-probability" AVC, psychological repercussions of young patients, and costs need to be considered before performing genetic screening[75].

DIFFERENTIAL DIAGNOSIS

Idiopathic RVOT-VT is a major non-hereditary differential diagnosis that has to be distinguished from ARVC/D. This is often demanding, particularly in the early stages of AVC[141]. RVOT-VT is not associated with structural heart disease and thus has a more benign course. Its etiology is unclear, although in one study a somatic point mutation in the inhibitory G protein Gai2 was identified by EMB from the arrhythmic focus[142]. In RVOT-VT, 12-lead surface ECG and SAECG are normal during sinus rhythm. It is characterized by repetitive monomorphic VT of a single morphology with LBBB morphology and an inferior axis. Similar VT morphologies can be found in patients with ARVC/D. 12-lead ECG scoring systems to differentiate both types of VT have recently been proposed[108]. In ARVC/D the duration of the QRS complex during VT is usually longer (≥ 120 ms in lead I)[143]. Notching of the QRS and precordial transition in lead V6 may exclusively be seen in ARVC/D[144]. RVOT-VT is difficult to induce by programmed ventricular stimulation during EPS, particularly in the absence of isoproterenol[87]. It responds well to beta-blockers or verapamil and ablation after successful mapping is usually curative. EAM demonstrates normal voltages. CPVT is caused by mutations in the *RyR2* gene, which has also been described in ARVC/D subtype 2. CPVT is characterized by effort-induced polymorphic VT in patients with structurally normal hearts. Genetic analysis, a positive family history, EAM and EMB can help to differentiate AVC and regional myocarditis[14]. Myocardial involvement in sarcoidosis can mimic ARVC/D and the

current TFC do not reliably distinguish between them. In a prospective study of patients with suspected ARVC/D, evaluated by a protocol including EMB, a surprisingly high incidence (15%) of cardiac sarcoidosis was verified[145]. Sarcoidosis with cardiac involvement thus always needs to be considered, particularly if respiratory and systemic symptoms, high-grade atrioventricular conduction block, and no family disease are present. Similar clinical presentations and imaging findings can pose a challenge in the absence of histological diagnosis. Features favoring cardiac sarcoidosis include early septal involvement, reduced LV function, a wide QRS during VT, right-sided apical VT and more inducible forms of monomorphic VT[146]. Diagnosis is usually confirmed by EMB[147]. In patients who survive SCD, ischemic heart disease and an anomalous origin of the coronary arteries have to be excluded. DCM is particularly difficult to distinguish from non-classic forms of AVC. Palpitations, (pre)syncope and ventricular arrhythmias are present at an early stage in AVC, often in the absence of gross structural abnormalities, which is usually not the case in DCM. Subepicardial LGE on CMR, particularly in the posterobasal LV wall, also favors AVC[36]. Atrioventricular conduction block is more common in DCM, but mutations in lamin A/C can cause AVC with conduction defects[148]. Bs may mimic ARVC as RV conduction delay has been demonstrated in both and recently a genetic overlap between these two entities has been proposed[94,149]. The presence of gross structural abnormalities favors AVC and mutations in SCN5A are very rare in AVC. Further differential diagnoses include RV infarction, pulmonary hypertension, congenital left-to-right shunts, Chagas disease and Uhl's disease (congenital hypoplastic RV).

DISEASE COURSE AND PROGNOSIS

Although AVC is a progressive disease, the individual disease course can vary considerably. The mortality rate is currently estimated to be around 1%-3% per year. In one study, after 8 years of mean follow-up, total mortality was approximately 20% and the mean age at death 54 ± 19 years. Most patients died of progressive heart failure (59%) and VTA (29%)[150]. Embolic stroke may lead to death in a smaller proportion of patients.

AVC occurs in four phases[2]: (1) concealed phase, during which patients are asymptomatic and structural abnormalities are absent or subtle. Nevertheless, AVC can present with SCD as the primary manifestation; (2) occurrence of symptomatic arrhythmias; (3) early heart failure symptoms; and (4) end-stage heart failure necessitating a ventricular assist device or cardiac transplantation. One study has shown that 7% of AVC patients received cardiac transplantation after a mean follow-up period of 10 years and severe LV involvement is often present in this population[7]. Strenuous physical activity often leads to early disease manifestation and rapid disease progression. Young competitive athletes with AVC have a 5-fold increased risk of SCD compared to non-athletes and identification of affected athletes by pre-participation screening has substantially reduced mortality in this cohort[64,151]. Interestingly, in one study, mutation-carrying female relatives were less frequently affected than male relatives. This has been interpreted as prevention of apoptosis in cardiac myocytes by estradiol but could also be related to more life-long physical activity in men[152].

RISK STRATIFICATION

SCD in patients with AVC is difficult to predict and often occurs without alarming symptoms. The only reliable strategy for SCD prevention is the implantation of an ICD, with an annual incidence of appropriate ICD interventions among AVC patients of 5%-22%, demonstrating its importance for these patients. Thus, in secondary prevention after aborted SCD, VF or sustained VT, ICD implantation is recommended[87,147]. Besides aborted SCD, VF and sustained VT, other potential risk factors for SCD or appropriate ICD therapy (a surrogate marker for SCD) have been suggested: (1) syncope (DARVIN 2 study)[93]; (2) left ventricular dysfunction[7,56,153]; (3) young age at presentation[62,63,67] and young age per se[47,64]; (4) RV structural abnormalities fulfilling 2010 TFC[47,154]; (5) severe tricuspid regurgitation[7]; (6) particular genetic variants[8,72]; (7) presence of non-sustained VT[155]; (8) male gender[79]; (9) proband status[79]; (10) frequent PVC[79]; and (11) presence of precordial T-wave inversions[79].

It is important to recognize that the use of appropriate ICD therapy due to sustained VT or VF as a surrogate for SCD can result in an overestimation of this endpoint. Whether in the absence of arrhythmic syncope or significant ventricular arrhythmias the other potential risk factors are consistently related to an adverse arrhythmic outcome and require prophylactic ICD therapy remains to be determined by future studies. Of note, young patients may suffer from neurocardiogenic syncope, making differential diagnosis difficult and its prognostic value elusive. T-waves in the precordial and inferior leads often become negative with progression of AVC and a greater extent of precordial negative T-waves are associated with more severe RV dilation and dysfunction[100]. Recently, the Johns Hopkins group found that 88% of patients with documented sustained VTA exhibited an abnormal ECG. A total of 122 (84%) subjects demonstrated T-wave inversions in the precordial leads with 97 of them extending to lead V3 and beyond, while depolarization abnormalities such as epsilon waves were present only in a minority of patients[156]. The same group found that the presence of T-wave inversions in ≥ 3 precordial ECG leads was an independent predictor of adverse events during follow-up[79]. An Italian group has also demonstrated a link between the extent of negative T-waves and ventricular arrhythmic events during follow-up[157]. Although a class Ⅱb recommendation, the role of EPS with programmed ventricular stimulation for risk stratification in AVC is less well established and conflicting data about its prognostic significance exist[45,64,90,158]. Differ-

ences in the studied patient population may be influenced by disease severity[159] and differences in study design may have led to discrepant results. A positive family history of SCD in asymptomatic patients does not seem to increase their individual risk for lethal arrhythmias. Guidelines do not support genetic testing for risk stratification in AVC[1] and genotype-phenotype correlation studies so far have not consistently been able to show that genotyping is able to detect mutations specifically associated with an increased susceptibility to life-threatening arrhythmic events. However, recent data indicates that certain pathogenic mutations (*e.g.*, plakoglobin in Naxos disease, RyR2 and TME-43) may increase the risk for SCD[8,62,67]. These preliminary results have to be confirmed in larger studies and more precise risk stratification tools for asymptomatic patients are needed. Novel imaging modalities such as strain and three-dimensional echocardiography could help to further improve risk stratification[160].

Based on the available data from observational studies, we suggest classifying patients into three risk categories[79,161]: (1) high risk: aborted SCD, sustained VT and VF, arrhythmic syncope; (2) moderate risk: non-sustained VT, severe structural abnormalities of RV and/or LV, presence of cardiac symptoms, $\geqslant$ 3 leads with T-wave inversions, frequent PVCs (*i.e.*, > 760 PVC/24 h Holter) and severe disease onset age < 35 years; and (3) low risk: asymptomatic family members (also despite a positive family history of SCD), < 10 PVC/24 h Holter.

The risk factors listed here have focused largely on patients with right-dominant disease. Prognostic factors in non-classic disease still remain elusive. Patients should be astute for symptoms. Dynamic T-wave inversions, ST segment elevation and myocardial biomarker release mimicking myocardial infarction should alert the treating physicians to think of a "hot phase" of AVC. Clinical evaluation starting at age 10-12 is suggested for all first- and second-degree relatives of AVC index patients until age 60[140]. If SCD occurs at age < 35, a full postmortem autopsy by an expert cardiac pathologist including molecular autopsy screening for genetic variants should be performed.

THERAPY

Physical activity restriction

It is a general consensus that strenuous physical activity should be avoided in symptomatic patients with AVC. There is no consensus that physical activity should be avoided in asymptomatic healthy gene carriers. A recent study has shown that endurance exercise and frequent exercise increase the risk of VT/VF and heart failure in patients, but also in healthy family members carrying a pathogenic desmosomal mutation, supporting exercise restriction for these patients[82]. We prudently advise all symptomatic patients and healthy gene carriers to refrain from practicing competitive sports and strenuous physical exercise, not only for reducing the risk of ventricular arrhythmias, but also to prevent disease onset and progression.

Pharmacological therapy

Beta-blockers, amiodarone and sotalol can be effective for treatment of sustained VT or VF in patients with AVC. However, they have no proven prognostic benefit such as ICD therapy. Wichter *et al*[107] proved that sotalol is highly effective to suppress VT by programmed ventricular stimulation with an efficacy of 68% and 83%, respectively, but had no effects on prognosis and SCD. Amiodarone was not superior to sotalol in this study and is not considered first-line therapy by many clinicians because of frequent side effects during long term therapy, particularly in young patients. However, recent data from the Northern American ARVC registry demonstrated amiodarone to confer the greatest efficacy in preventing ventricular arrhythmias when compared to sotalol or beta-blockers. However, mean sotalol doses were lower than in the study from Wichter *et al*[107] and only ten patients were treated with amiodarone in the American study. In clinical practice, beta-blockers, sotalol or amiodarone are often used as an adjunctive therapy to reduce arrhythmia burden in patient with an ICD and amiodarone is sometimes combined with beta-blockers in order to reduce sympathetic tone and mechanical wall stress[162]. Co-administration of sotalol and amiodarone is not recommended due to QT interval prolongation. Hiroi *et al*[163] suggest that carvedilol may control arrhythmias and improve LV function in some patients with biventricular AVC. Calcium antagonists such as verapamil and mexiletin may be effective in some patients to suppress VT but data is anecdotal. If heart failure occurs, standard therapy with beta-blockers, angiotensin converting enzyme-inhibitors and a diuretic should be established, although there are no specific studies in patients with AVC[46]. Brain natriuretic peptide, C-reactive protein, IL-1β and TNF-α as surrogate biomarkers for disease activity, inflammation and prognosis have been advocated in AVC but await further validation[3,58,164]. AVC patients at later stages have an increased risk for thromboembolism[43]. The annual incidence of thromboembolic complications, including pulmonary embolism, RVOT thrombosis and cerebrovascular events, was 0.5% in a retrospective study of 126 patients followed up for a mean period of 99 ± 64 mo[56]. Anticoagulation is often started by clinicians in the presence of severe ventricular dilation, dysfunction and aneurysm, although existing studies do not support prophylactic use in those with RV aneurysms. Data for the non-classic subtypes are lacking.

Implantable cardioverter-defibrillator

According to the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities and its recent update[165,166], ICD implantation is indicated in patients with structural heart disease who have experienced a sustained VTA (secondary prevention, Class I indication). It is also stated that ICD implantation is reasonable in AVC patients who have at least one

risk factor for SCD (Ⅱ A indication, level of evidence C). Thus, ICDs constitute a cornerstone for those patients and can prolong survival in this population. In fact, a large number of studies has demonstrated that patients with AVC who undergo ICD implantation have a high likelihood for appropriate ICD therapies[167]. However, many questions remain regarding AVC patients and their relatives who are at low to moderate risk for SCD. In these patients, a lifelong risk for lethal arrhythmias has to be weighed against the complication rates of ICDs, inadequate interventions (up to 24% within 5 years), psychological burden and economic costs of this therapy. However, complication rates seem to have declined since the use of third- or fourth-generation defibrillators. Active and young patients are at particular risk of lead displacement and inappropriate discharges for sinus tachycardia, including painful shocks and multiple invasive procedures. Thus, indiscriminate device implantation cannot be endorsed. Instead, reliable risk stratification is of paramount importance. An ICD with dual chamber detection algorithms may be wise in young patients to discriminate VT or SVT from sinus tachycardia. The use of antiarrhythmic agents can also reduce the number of inadequate interventions due to supraventricular tachyarrhythmias. Furthermore, programming of higher VT/VF cut-offs and longer detection intervals can avoid inappropriate ICD shocks[168]. Complications of ICD therapy include a risk for perforation caused by thinning of the RV wall, lead dislodgement, R wave under-sensing and high pacing thresholds. As patients are young and mobile, these risks need particular consideration, although in one study, short and long-term risks of ICD therapy were similar to patients without AVC[45].

In our clinical routine, we recommend ICD implantation for all AVC patients who have experienced a sustained VTA but we also carefully evaluate ICD implantation for primary prevention in probands and family members without documented sustained VTA. Therefore, we evaluate whether a particular patient (1) has high-risk features for SCD during follow-up (see list above), (2) whether the patient is willing to take his medication regularly and to stop competitive sports (*i.e.,* competitive individual events like triathlon or participation in a competitive sports team), and (3) the patient's preferences. Our threshold for ICD implantation is higher in family members and asymptomatic patients owing to the fact that previous studies have consistently shown that family members are at lower risk of experiencing sustained VTA. A possible explanation for this finding is that diagnosis occurs earlier in the disease course and once diagnosed, family members are encouraged to give up competitive sports. However, more data obtained from different well characterized AVC cohorts are necessary to assist clinicians in guiding ICD therapy.

Catheter ablation

Catheter ablation was first applied to treat drug-resistant VT. The application of direct current (DC) termed fulguration, used DC from a defibrillator to burn myocardial sites responsible for abnormal ventricular activation. The electric voltage was directly delivered through a catheter to the origins of VT. However, this procedure was associated with a significant risk of complications and thus rapidly abandoned. Currently accepted indications for radiofrequency catheter ablation in patients with AVC include drug-refractory VT or incessant VT with frequent ICD shocks. It should be kept in mind that, unlike in patients with idiopathic VT where catheter ablation is curative, catheter ablation in patients with AVC can only improve quality of life by decreasing the number of VT episodes and PVCs[169]. Catheter ablation can follow a trial of beta-blocker therapy and antiarrhythmic therapy. In some patients who do not wish long-term therapy with beta-blockers, sotalol and particularly amiodarone, catheter ablation can be performed as first line therapy. Elimination of clinical tachycardia can relieve symptoms but may not prevent SCD.

Over the last years, mapping and ablation techniques have made outstanding progress and nowadays include activation, pace and entrainment mapping during VT and substrate-based ablation using EAM that can be performed *via* an endocardial and epicardial approach[170]. Substrate-based ablation of PVCs and VT is particularly important when conventional mapping during tachycardia is not possible due to hemodynamic instability or multiple VT morphologies[171]. Although the initial approach involved extensive mapping to identify critical zones of slow conduction during VT, this approach has recently been replaced by a substrate-based approach. Preliminary studies have shown promising results regarding safety, arrhythmia-free survival and reduction of ICD discharges, particularly if an endocardial and epicardial approach are combined[128-131]. In one recent study from the Johns Hopkins cohort, the overall freedom from VT was 47%, 21% and 15% at 1, 5 and 10 years, respectively. Following epicardial VT ablation, the cumulative freedom from VT was 64% and 45% at 1 and 5 years. Of note, the VT burden decreased from a median of 0.16 VT episodes per month pre ablation to 0.08 episodes per month post ablation[172]. Mid-term and long-term success and safety of these methods have to be demonstrated in future studies with larger cohorts.

Surgical methods

Total surgical electrical RV disconnection carries an important risk of postoperative RV failure and has been practically abandoned[173]. If severe therapy refractory heart failure occurs, ventricular assist devices or heart transplantation have to be considered for isolated LV or biventricular failure and less frequently isolated RV failure. Some authors suggest that right heart catheterization should be performed in all cases with suspected severe RV dysfunction. If increased filling pressures suggest a Fontan-type physiology, the patient may be considered for heart transplantation[174].

CONCLUSION

During the last three decades, our understanding of AVC from a developmental RV dysplasia with substitution by adipose tissue has remarkably changed to a mostly inherited polygenic disease of the intercalated disk with a broad phenotypic spectrum. Although AVC predominantly affects the RV, non-classic forms affecting the LV or both ventricles are increasingly recognized. A hallmark is the early propensity to ventricular arrhythmias associated with SCD at a young age. Enormous progress in unravelling the genetic and molecular basis of this complex disease, in which environmental factors seem to play a pivotal role, has been made in the last years. While progress in imaging and device therapy has facilitated clinical diagnosis and prevention of SCD, today's challenges include discovery of novel genetic and environmental factors, early detection of asymptomatic patients, improved risk stratification, catheter ablation strategies and causal therapies to cure the disease[175]. Multicenter, large, prospective follow-up studies are planned to improve our understanding of the complex underlying molecular mechanisms of AVC, which may facilitate diagnosis, risk stratification and causal therapy.

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