Arrhythmogenic Cardiomyopathy

Aritmogena kardiomiopatija

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Abstract

Arrhythmogenic cardiomyopathy (AC) is a genetic disease of the myocardium characterized by fibro-fatty replacement of the apoptotic myocardium. It primarily affects the right ventricle, however in advanced stages of the disease the left ventricle can also be significantly affected.

AC is a challenging diagnosis, especially in the early stages of the disease, and should be considered in all patients presenting with palpitations, syncope or sudden cardiac death when other, more common causes of these symptoms/signs are excluded. In patients with suspected AC, evaluation according to the current Task Force Criteria should be applied to achieve optimal diagnostic yield.

The main therapeutic concern in AC patients is the prevention of SCD, and thus all patients with established diagnosis have to be evaluated for potential ICD implantation, which is indicated in the majority of symptomatic patients.

In this narrative review we aim to outline current knowledge on the pathophysiology, diagnosis and treatment strategies of AC.

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Izvleček

Aritmogena kardiomiopatija desnega prekata (AC) je genetska bolezen srčne mišice, za katero je značilna maščobno-vezivna infiltracija prizadetega miokarda. Primarno prizadene desni prekat, v pozni fazi bolezni pa je navadno prizadet tudi miokard levega prekata.

AC je pogosto zahtevno diagnosticirati, še posebej v zgodnjih fazah bolezni. Zaradi nespecifičnih simptomov in znakov je na AC potrebno diferencialnodiagnostično pomisliti pri vsakem bolniku, ki prihaja v kardiološko obravnavo zaradi palpitacij, sinkope ali pa malignih motenj srčnega ritma. Bolnike s sumom na AC je potrebno obravnavati po trenutnih merilih Task Force, saj lahko le tako zagotovimo standardizirano obravnavo teh bolnikov.

V preglednem članku predstavljamo trenutno znanje o patofiziologiji, diagnosticiranju in strategijah zdravljenja AC.

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1 Introduction

Arrhythmogenic cardiomyopathy (AC) is a genetic myocardial disease with an estimated prevalence from 1 in 1,000 to 1 in 5,000 (1,2). In the past, the disease was more commonly referred to as arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). However, the recognition of frequent left ventricular (LV) involvement led to the change in the nomenclature of the disease; now the preferred term is arrhythmogenic cardiomyopathy. The disease is characterised histologically by progressive fibro-fatty replacement of predominantly right ventricular (RV) myocardium and clinically mainly by ventricular arrhythmias and RV, and in later stages LV, dysfunction with or without associated heart failure (3). Most commonly patients develop symptoms and signs of the disease between the second and fourth decade.

AC is commonly underlined by mutations mainly in genes coding cardiomyocyte structural proteins. Inadequate intercellular connections result in progressive fibro-fatty replacement of the myocardium, which in turn creates a favourable environment for ventricular arrhythmias. Importantly, sudden cardiac death may be an initial presentation of AC and current data suggest that 6.4 % of all sudden cardiac deaths may be attributed to AC (4,5). Although there are many diagnostic tools that help us establish the diagnosis of AC, they all lack sensitivity and specificity for early disease detection (6).

In this narrative review we aim to outline current knowledge on the pathophysiology, diagnosis and treatment strategies of AC.

2 Genetics and pathogenesis of AC

AC is most commonly inherited as an autosomal dominant disorder with reduced genetic penetrance and variable expression, however autosomal recessive inheritance has also been described (7,8). Up to 30 % of first-degree relatives of patients with AC may be at risk of developing the disease (9). Men are affected more frequently than women with an estimated ratio of 3:1 (10).

Twelve different genes on 9 chromosomes are currently known to be involved in the pathogenesis of the disease. Most of them code structural proteins, mainly adhesion proteins such as plakoglobin, plakophilin-2, desmoplakin and desmoglein-2 (7,8,11,12). Additionally, genes coding for non-structural proteins have been implicated in the pathogenesis of AC, including ryanodine-2 receptor, transforming growth factor-β3 and connexin 43 (13-15). Recently, mutations in gene coding LIM domain-binding protein 3 (a factor that plays an important role in maintaining the structural integrity of the striated muscle Z-disc) were also associated with AC (16,17).

Currently it is believed that mutations in plakophilin-2 (PKP2) gene account for around 40 % of AC cases (18,19). In familial cases of the disease this percentage may even be higher (up to 70 %). However, as variable expression and penetrance of PKP2 gene was shown in first-degree relatives, any predictions of AC occurrence in the carriers of the mutated PKP2 gene are difficult to make (20).

Three hypotheses were proposed explaining the pathogenesis of fibro-fatty transformation of the myocardium

in AC. According to the first, in individuals with mutated genes for desmosomal proteins, cardiomyocyte attrition and fibro-fatty replacement occur mainly due to mechanical shear stress that induces apoptosis in inadequately attached cardiomyocytes (7,8,11,16). The second hypothesis implies a viral infection as an initial trigger that worsens the already structurally impaired myocardium (21,22). Regardless of the initial trigger, subsequent inflammatory response in the myocardium propagates the process of fibro-fatty myocardial transformation and the development of macro-reentry circuits. A study from Mersmann et al. showed that inflammatory cells may by themselves represent potential triggers of ventricular arrhythmias through toll-like receptor pathways (23). A third hypothesis proposes an altered (increased) expression of pro-fibrotic and adipogenic proteins in the cardiomyocytes in response to the altered expression of cardiomyocyte structural proteins which in turn leads to cardiomyocyte apoptosis and fibro-fatty replacement of the myocardium (1). Data also suggest that gap junctions may be involved in the pathogenesis of AC (through mutations in gene coding connexin 43 gap-junction protein), which could result in slower myocardial conduction, thus facilitating the occurrence of ventricular arrhythmias (1,24,25).

The most commonly affected areas of the myocardium are the inflow and outflow portions of RV, followed by an apical involvement (also known as the triangle of dysplasia). The RV wall progressively becomes thinner and aneurysms may occur. Epicardial or mid-wall segments of the RV wall are initially affected. In later stages of the disease, however, the involvement of the RV wall becomes transmural (26,27,28). Importantly, rather than being a continuous, ongoing process, disease progression may occur through periodic bursts of otherwise stable disease. Although the name arrhythmogenic right ventricular cardiomyopathy used to imply that the RV is exclusively affected, LV involvement (most commonly posterolateral portion) is also commonly present in patients with advanced stages of the disease (in up to 50 % of patients) (15,27,28). Hence the term AC is more appropriate.

3 Clinical presentation

The classical right-sided natural history of AC typically follows four stages: the initial phase is named *concealed* because there are no or only subtle changes in RV structure and function with or without minor ventricular arrhythmias. Nevertheless, SCD can occur at this early stage as the first manifestation of the disease in previously healthy young individuals. The second phase of clinically overt disease is characterised by RV arrhythmias, palpitations, syncope or SCD that are associated with a manifest RV functional and structural dysfunction that is detectable by imaging tests. In the third phase, signs of RV failure develop whereas LV function remains largely preserved. The fourth stage is characterised by a "burnout" biventricular failure. At this point, AC may resemble dilated cardiomyopathy of other causes (10,29).

Ventricular arrhythmias may present as paroxysmal palpitations in 27 %, 26 % of patients with AC initially present as syncope, and in up to 23 % of AC patients sudden cardiac death may be an initial presentation of the disease. Arrhythmias can range from isolated premature ventricular beats to ventricular tachycardia of left or right bundle branch block morphology or ventricular fibrillation (3,6,30).

Symptoms and signs of heart failure (predominantly right heart failure) are standard and non-specific to AC and include peripheral edema, ascites, hepato-splenomegaly and pleural effusions which are usually accompanied by a progressive decrease in exercise capacity and, in advanced stages of the disease, cardiac cachexia.

Importantly, the described symptoms and signs of AC at any stage of the disease are non-specific, thus making the diagnosis of early AC challenging.

4 Diagnosis

AC should be considered in all patients presenting with palpitations, syncope or sudden cardiac death when other, more common causes, such as ischaemic heart disease or valvular heart disease, are excluded. For the routine screening and assessment of AC detailed patient history evaluation and clinical examination should be performed, followed by 12-lead and/or Holter ECG and transthoracic echocardiography (32). If these non-invasive methods are inconclusive, more specific imaging modalities such as contrast-enhanced cardiac magnetic resonance imaging and/or rarely endomyocardial biopsy are needed. Recently, a consensus statement regarding comprehensive multi-modality imaging approach in AC was published by the European Association of Cardiovascular Imaging that for the first time gives clinical recommendations for how to use multimodality imaging in different aspects and stages of AC (33).

4.1 Task Force Criteria

Until recently, the original Task Force Criteria (TFC) was the gold standard for diagnosing AC but these criteria lacked quantitative assessment modules and genetic criteria. Accordingly, in 2010 the original Task Force Criteria were modified and should now represent the framework for the diagnosis of AC (Table 1). The criteria are divided into major and minor subgroups depending on their specificity for AC. Diagnosis is established when two major plus two minor or one major plus four minor criteria from different groups are fulfilled (34). Cox et al. showed that the modifications of the original TFC were promising as the application of modified criteria identified additional 64 % probable AC patients, and 11 % family members of AC patients were additionally diagnosed with the disease (35).

In a recent study, Femia et al. compared the old and new Task Force Criteria using cardiac magnetic resonance (CMR). Their results showed that the new criteria have enhanced the diagnostic potential of CMR. For both major and minor CMR criteria the negative predictive values have not changed and stayed at 100 % but the positive predictive values have improved from 23 % to 55 % (36). Despite the modified AC criteria, the diagnosis remains challenging, particularly in early stages of the disease, because of the low specificity of electrocardiographic abnormalities, multiple causes of RV arrhythmias, difficulties in the use of imaging modalities to evaluate RV structure and function and the often puzzling and inconclusive results of genetic testing. Better understanding of pathophysiological mechanisms involved in AC is of paramount importance to develop more specific criteria for the diagnosis of AC.

4.2 Electrocardiography

Because electrocardiographic (ECG) abnormalities may be detected long before any clinical, functional or his-

Table 1: Modified Task Force diagnostic criteria for AC (46).

	Major	Minor

1. Global and/or regional dysfunction and structural alterations	By 2D echo:
	• Regional RV akinesia, dyskinesia, or aneurysm
	• *and* 1 of the following (end diastole):
	  • PLAX RVOT ≥ 32 mm (corrected for body size (PLAX/BSA) ≥19 mm/m^2)
	  • PSAX RVOT ≥ 36 mm (corrected for body size (PSAX/BSA) ≥21 mm/m^2)
	  • *or* fractional area change ≤ 33 %
	By MRI:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
	• *and* 1 of the following:
	  • Ratio of RV end-diastolic volume to BSA ≥ 110 mL/m^2 (male) or ≥ 100 mL/m^2 (female)
	  • *or* RV ejection fraction ≤ 40 %
	By RV angiography:
	• Regional RV akinesia, dyskinesia, or aneurysm
		By 2D echo:
		• Regional RV akinesia or dyskinesia
		• *and* 1 of the following (end diastole):
		  • PLAX RVOT ≥ 29 to < 32 mm (corrected for body size (PLAX/BSA) ≥16 to < 19 mm/m^2)
		  • PSAX RVOT ≥ 32 to < 36 mm (corrected for body size (PSAX/BSA) ≥18 to < 21 mm/m^2)
		  • *or* fractional area change > 33 % to ≤ 40 %
		By MRI:
		• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
		• *and* 1 of the following:
		  • Ratio of RV end-diastolic volume to BSA ≥ 100 to < 110 mL/m^2 (male) or ≥ 90 to < 100 mL/m^2 (female)
		  • *or* RV ejection fraction > 40 % to ≤ 45 %

2. Tissue characterisation of RV wall	• Residual myocytes < 60 % by morphometric analysis (or < 50 % if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60 % to 75 % by morphometric analysis (or 50 % to 65 % if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
3. Repolarisation abnormalities	• Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals > 14 years of age (in the absence of complete right bundle-branch block - QRS ≥ 120 ms)	• Inverted T waves in leads V1 and V2 in individuals > 14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 • Inverted T waves in leads V1, V2, V3, and V4 in individuals > 14 years of age in the presence of complete right bundle-branch block
4. Depolarisation/ conduction abnormalities	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)	• Late potentials by Signal-averaged ECG (SAECG) in ≥ 1 of 3 parameters in the absence of a QRS duration of ≥ 110 ms on the standard ECG • Filtered QRS duration (fQRS) ≥114 ms • Duration of terminal QRS < 40 µV (low-amplitude signal duration) ≥38 ms • Root-mean-square voltage of terminal 40 ms ≤ 20 µV • Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete right bundle-branch block
5. Arrhythmias	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • > 500 ventricular extrasystoles per 24 hours (Holter)
6. Family history	• AC confirmed in a first-degree relative who meets current Task Force criteria • AC confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation† categorized as associated or probably associated with AC in the patient under evaluation	• History of AC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected AC in a first-degree relative • AC confirmed pathologically or by current Task Force Criteria in second-degree relative

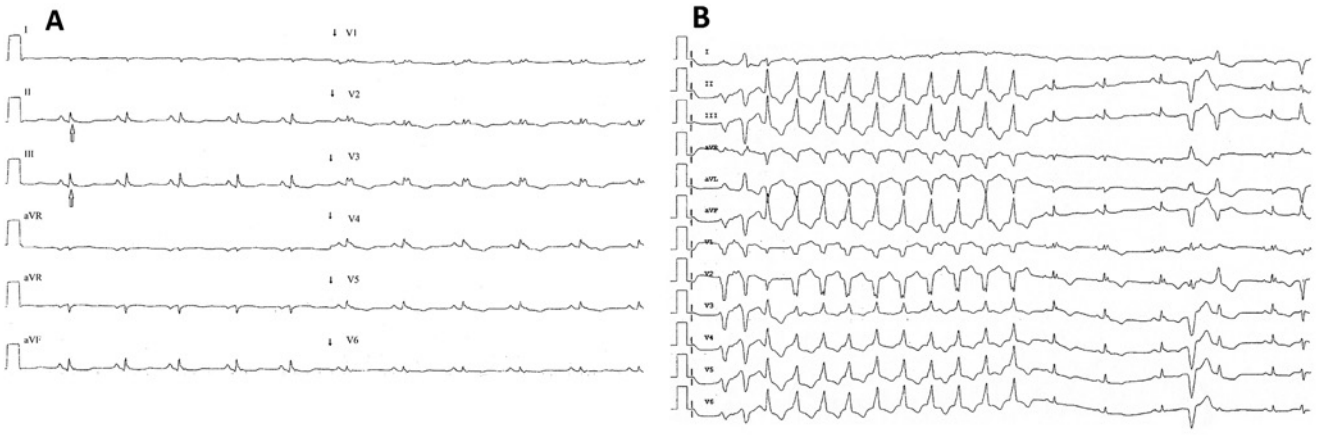

Figure 1: 12-lead electrocardiographic tracing showing a patient with AC; In panel A the patient is in sinus rhythm, and ECG is remarkable for wide QRS (150 ms), RSR' morphology and epsilon wave (arrow) at the end of the QRS. This signifies slow intramyocardial conduction and not a disease of the right bundle branch. A T-wave inversion in precordial leads is also present (V1-V6). In panel B a non-sustained VT was recorded in the same patient.

tological signs of the disease, ECG is a valuable tool in the diagnostic process of AC (37,38). The main differential diagnosis of AC is idiopathic RV outflow tachycardia (RVOT-VT). The latter is of benign nature and has an indolent course and thus should always be differentiated from AC. Baseline sinus rhythm ECG and electrocardiographic differences during ventricular tachyarrhythmias (VT) or premature ventricular beats can be helpful in the differentiation of the two pathologies (6). T wave inversion, epsilon waves and multiform ventricular tachycardia are the most important ECG findings characteristic for AC.

In baseline sinus rhythm the presence of T wave inversion in V1–V3 may aid the diagnosis of AC, but data suggest that these changes may only be present in 32 % of AC patients as well as in 1–3 % of normal young patients and 4 % of RVOT-VT patients (6,39,40,41,42).

Epsilon waves (low-amplitude signals between the ends of the QRS complex before the beginning of the T waves) in right precordial leads are pathognomonic and represent a major diagnostic criterion. Nevertheless, this finding is only present in the minority (up to 37 %) of AC patients (39,43,44). Additionally, the interobserver variability in the assessment of epsilon waves is rather high (45).

Early in the course of the disease monomorphic VTs can most commonly be seen. If more than one form of VT is present, it increases the probability for AC and reflects a more diffuse involvement of the RV myocardium. An exemplary ECG of AC patient is presented in Figure 1.

4.3 Echocardiography

Echocardiography is one of the essential first-line tools for diagnosing AC and has gained its clinical value with the revised Task Force Criteria (46). The major criteria were designed to yield 95 % specificity and require regional RV akinesia/dyskinesia or aneurysm in conjunction with either RV outflow dilatation or reduced fractional area change. Minor criteria were selected to yield sensitivity equal to specificity (47).

Yoerger et al. compared echocardiograms from 29 AC patients with echocardiograms from 29 normal control pa-

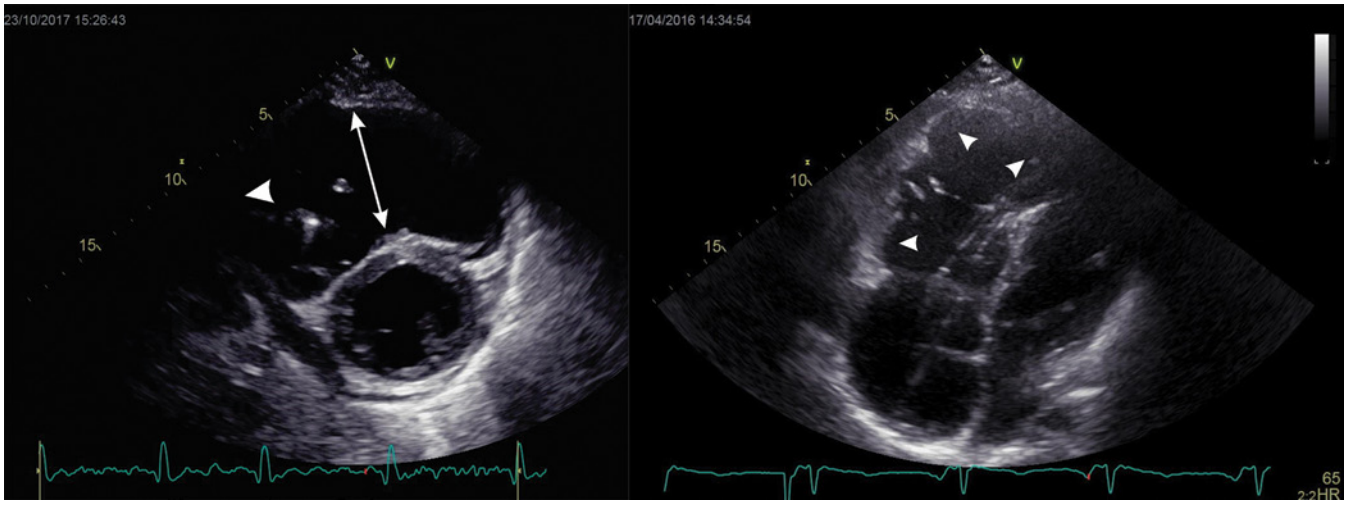

Figure 2: Representative echocardiography images of AC; Panel A shows a parasternal short axis view of enlarged right ventricular cavity (white arrow showing an increased RV diameter, arrowhead showing a right ventricular aneurism); Panel B shows a 4-chamber view of enlarged right ventricle with multiple aneurisms (arrowheads).

tients matched for age, gender, body size, and year of examination. In AC patients, RV dimensions were significantly increased (27.2 ± 16 mm vs. 41.0 ± 7.1 mm, P = 0.0003), and RV fractional area change was significantly decreased in comparison to controls (Figure 2A). The RV outflow tract (RVOT) was the most commonly enlarged dimension (37.9 ± 6.6 mm in AC patients vs. 26.2 ± 4.9 mm in controls, P < 0.00001). A RVOT long-axis diastolic dimension > 30 mm occurred in 89 % of AC patients and in 14 % of controls. The RV wall morphological abnormalities (trabecular derangement in 54 %, hyper-reflective moderator band in 34 % and sacculations in 17 %) were present in significant proportion of the AC patients but not in controls (Figure 2B) (48).

Novel echocardiographic techniques may improve the performance of standard 2D echocardiography. Regardless of some technical limitations, Doppler tissue imaging has been proven useful in the assessment of RV longitudinal systolic function in AC patients (33,49). RV function can be further assessed by speckle tracking echocardiography, traced from the 4-chamber view with the focus on RV. RV peak systolic longitudinal strain from 6 RV segments are averaged to calculate RV global longitudinal strain. Alternatively, peak systolic strain from 3 RV free wall segments are averaged as a measure of RV free wall strain, which often results in higher absolute values than RV global longitudinal strain. Both measures have been reported to be already reduced in early phases of AC and can be very useful in the differential diagnostics of AC as well as in the risk stratification of AC patients (50). In addition to amplitude parameters, temporal parameters, such as time-to-peak strain, can also be of use in evaluating patients with AC as RV mechanical dispersion is increased in this patient cohort (50).

3D echocardiography offers some further advantages in diagnosing AC as it allows for better measurement of RV volumes and regional wall motion abnormalities than 2D echocardiography. RV and LV volumes are of interest espe-

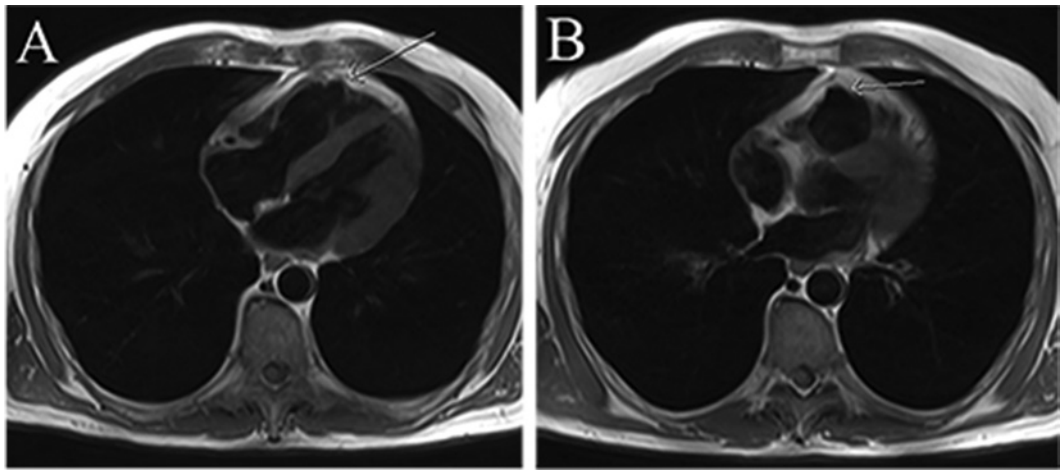

Figure 3: Representative CMR axial view (Spin echo T1 'black blood' sequence) of the heart in an AC patient. In panel A and B dyskinesia and bulging of thin RV wall is seen (arrows).

cially in patients with overt AC, whereas increased volumes are only rarely seen in early phases of AC. 3D echocardiography is mainly limited by its need for good image quality which can be difficult to obtain in AC patients with severely enlarged RV and should thus be used in laboratories with appropriate 3D platforms and experience in this imaging modality (50).

4.4 Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) imaging is included in the major and minor Task Force Criteria and represents a valuable method in diagnosing AC. The modified TFC does not only include qualitative measurements (e.g. regional RV akinesia or dyskinesia or dyssynchronous RV contraction) but also quantitative parameters (e.g. ratio of RV end-diastolic volume to body surface area). Additionally, it was shown that late enhancement on CMR has excellent correlation with histopathology and predicts ventricular tachycardia on programmed electrical stimulation (51) (Figure 3). CMR was also proven to have a diagnostic value in paediatric population as nearly 50 % more patients could be assigned to the definite group according to TFC by using CMR (52).

Overall CMR sensitivity for AC is reported to be around 90 % and specificity around 80 % (49,53). However, a novel methodology in the diagnosis of AC uses strain analysis by feature-tracking CMR. It was shown that analysis by feature-tracking helps objectively quantify global and regional RV dysfunction and RV dyssynchrony, potentially improving the sensitivity and specificity of CMR in diagnosing AC (54).

4.5 Genetic testing

Genotype-phenotype studies showed that mutation screening is of major importance in diagnosing AC especially in familial AC. It enables early identification of symptom-free patients that need regular clinical and imaging follow-up (Table 2). On the basis of genetic testing the patients can also be advised to avoid competitive sports, which is of paramount importance to prevent sudden cardiac death in this patient cohort (3). In non-familial AC, genetic testing in-

terpretation is more challenging as missense mutations in one of the major AC susceptibility genes were found in 16 % of healthy individuals (55). In addition, a mutation in an unknown disease-causing gene can result in a negative test result in a patient with characteristic AC phenotype (56).

4.6 Other diagnostic modalities

If noninvasive diagnostic methods are inconclusive, invasive methods may be indicated such as: RV ventriculography, electroanatomic mapping and endomyocardial biopsy. These invasive procedures were frequently employed in the past, but are presently indicated only in selected patients, in which the diagnosis of AC cannot be readily made with current state-ot-the-art noninvasive diagnostic modalities (55,57).

4.7 Future perspectives

In the future, the development of other promising diagnostic tools, such as equilibrium radionuclide angiography (ERNA) and immunohistochemical analysis for plakoglobin, have shown promising results (58,59). Taking in consideration that cardiac biopsy is rarely performed, immunohistochemical analysis for plakoglobin could be beneficial as an additional diagnostic marker, but validation of this methodology is still required. On the other hand, ERNA has shown significant diagnostic potential. It has a performance similar to that of echocardiogrpahy and CMR though further investigation is still needed

Table 2: Proposed follow-up and imaging intervals in patients with definite AC diagnosis and in family members (mutation positive or fist-degree relatives from families without identified mutations. CMR – cardiac magnetic resonance; CT-computer tomography; (33)

	Echocardiography	CMR	CT
AC patient with ICD	First visit, then when clinically indicated by heart failure symptoms.	Not indicated or contraindicated	/
AC patient without ICD	First visit, then every year or when clinically indicated.	First visit then every 3–5 years or when changes in clinical status or ECG occur. In patients who are difficult to explore by echo.	Patients who are difficult to assess by echo and unsuitable for CMR.
Family members with borderline findings	Every year in subjects < 40 years or when clinically indicated. Every 2 years in subjects > 40 years or when clinically indicated.	First visit, then every 1–2 years in subjects < 40 years or when clinically indicated. Every 3–5 years in subjects > 40 years or when clinically indicated.	Patients who are difficult to assess by echo and unsuitable for CMR.
Family members without any morphological findings	Every 1–2 years in subjects < 40 years or when clinically indicated. Every 3–5 years in subjects > 40 years or when clinically indicated.	First visit then every 1–2 years in subjects < 40 years or when clinically indicated. Every 3–5 years in subjects > 40 years or when clinically indicated.	Patients who are difficult to assess by echo and unsuitable for CMR.

to show whether it is superior to current diagnostic methods of AC (58,59).

4.8 Differential diagnosis or arrhythmogenic cardiomyopathy

Several other clinical entities, such as RV outflow tract tachycardia (RVOT-VT), cardiac sarcoidosis/myocarditis, athlete's heart and even dilated cardiomyopathy, may resemble AC. As these conditions are treated differently and, importantly, have different short- and long-term prognosis, it is important to establish a correct diagnosis.

4.8.1 RVOT-VT

The RVOT is the most common site of the origin of the idiopathic VT and premature ventricular complexes in patients with structurally normal hearts. In contrast to AC, RVOT-VT is most commonly a benign condition where VTs do not result in the haemodynamic compromise of the patient (33). However, as RVOT may also be a source of VTs in patients with early stages of AC, the distinction to RVOT-VT may be challenging. As the treatment and the prognosis between the two conditions differ significantly, an incorrect diagnosis may be devastating to the patient. By cardiac imaging, fibro-fatty myocardial replacement, a hallmark of AC, is not present in patients with RVOT-VT. Additionally, any findings of regional RV hypo- or dyskinesia in addition to RVOT dilatation make the diagnosis of AC more probable and the prognosis more severe (60). Other relevant tests include family history (usually normal in RVOT-VT), genetic testing and Holter monitoring. On 12-lead ECG T-wave inversion in the precordial leads, seen in AC, is absent in RVOT-VT patients. Additionally, high number of ventricular premature complexes (more than 9000/day) in the absence of structural heart disease supports the diagnosis of RVOT-VT over AC (50). In cases where the distinction between the two conditions cannot be made using noninvasive diagnostic modalities, electromechanical mapping of the RV and endomyocardial biopsy can be employed to differentiate between the two conditions.

4.8.2 Cardiac sarcoidosis and acute myocarditis

When compared to patients with AC, patients with cardiac sarcoidosis or acute myocarditis have several significantly different cardiac imaging findings. The degree and location of the cardiac involvement as well as cardiac volumes can be utilised to distinguish between these conditions. The presence of mediastinal lymphadenopathy, LV septal scarring, LV dysfuntion, and intense PET-FDG uptake in the myocardium should raise the suspicion for cardiac sarcoidosis, especially if other clinical features of sarcoidosis, such as conduction abnormalities or signs of pulmonary sarcoidosis are present (61). In patients with acute myocarditis LV is most commonly involved and RV is rarely selectively affected (33). Areas of segmental perfusion defects coupled with FDG uptake, local oedema, epicardial or midwall scarring and the presence of global or segmental hypokinesia not conforming to specific coronary territory distribution favour the diagnosis of acute myocarditis when clinically suspected (62).

4.8.3 Dilated cardiomyopathy

Distinguishing dilated cardiomyopathy (DCM) from atypical AC (biventricular or left-dominant) can be challenging. Echocardiography has a limited role in this setting, as LV dilatati-

on and systolic dysfunction are non-specific findings, present in both conditions. In left-dominant variant of AC LV structural and functional abnormalities are mainly localised in the posterolateral segment of the LV (33). CMR may offer better aid to the diagnosis of AC over DCM and vice-versa by providing tissue characterisation and identification of intramyocardial fat and fibrosis in addition to providing information on LV morphology and function.

4.8.4 Athlete's heart

RV and right atrial enlargement are not specific to AC, but may be found quite commonly in high-intensity exercise performing athletes. Additionally, in this population mild functional tricuspid regurgitation and dilatation of the inferior vena cava may be found (63). These echocardiographic findings resemble the ones found in AC patients and can make it challenging to distinguish between the two entities. Moreover, athletic activity worsens structural disease in AC patients, which further complicates the differentiation between AC and athlete's heart (33). RV dilatation in athletes preferentially involves RV inflow tract and is almost always associated with LV enlargement (balanced enlargement) (64). Characteristic findings in AC, like RV thinning, bulging and aneurysms are normally not present in athletes. Furthermore, RV TAPSE and strain measurements are typically normal in athletes even when RV dilatation is present, which is in contrast to AC patients where RV dilatation is typically accompanied by a decrease in RV systolic performance (65). Additionally, LV global longitudinal strain is most often normal in athletes (64). If AC is suspected in athletes, CMR must always be performed.

5 Patient Follow-Up and Screening of Family Members

Patients with AC and their family members should undergo regular (in case of patients life-long) clinical and imaging follow-up, preferably at the centres with the experience in managing patients with AC. Follow-up intervals and imaging modality used differ between AC patients and family members. As there is yet no consensus established on this issue, the recommendations for follow-up and imaging in AC patients and their relatives are largely dependent on cost-effectiveness and centre-specific capabilities. The proposed follow-up intervals and imaging methods are outlined in Table 2.

Current guidelines recommend that the initial genetic testing within a family should only be applied when an index patient has confirmed AC with an unequivocal phenotype (66). Within a family in which a patient has been diagnosed with AC there are three scenarios applicable to family members: the presence of a clear pathological mutation, absence of a clear pathological mutation and the presence of a DNA variant of uncertain significance. If a clear mutation is found in an index patient, then a cascade screening of family members helps to identify others at higher risk for developing AC. In case of an absence of a clear mutation in an index patient, AC is still regarded as a genetic disorder and all first-degree relatives should undergo *phenotypic* testing. In this scenario genetic testing is not mandatory as it may identify novel sequence variants without clear significance of pathogenicity. Importantly, family members with a negative phenotype but positive genotype are also advised to avoid endurance or

competitive sports because of the age--related penetrance and progressive nature of AC (67).

6 Prognosis

Determining the prognosis in AC patients is complex, and risk stratification has still not reached a wide consensus. The leading causes of death in patients with AC are ventricular tachyarrhythmias and congestive heart failure (68). The annual mortality estimates vary between different studies but are currently reported to be less than 1 % in community-based cohorts (36,37,38).

The factors most frequently associated with poor outcome in AC patients are: RV dysfunction, history of aborted cardiac death or ventricular fibrillation, syncope, young age at presentation, malignant family history, participation in competitive sports, history of ventricular tachycardia, significant tricuspid regurgitation, QRS dispersion of 40 ms or more, negative T-wave beyond V1, biventricular involvement, and the need for amiodarone treatment (68,69,70,71,72).

With regards to biomarkers in patients with AC it was found that plasma bridging integrator 1 (BIN1) level seems to correlate with the disease severity. Mean plasma BIN1 levels were decreased in patients with AC and associated heart failure. BIN1 levels also correlated inversely with the burden of previous ventricular arrhythmias. Low BIN1 levels also predicted future ventricular arrhythmias. These data are certainly encouraging but need verification in a larger clinical trial (73).

Animal data suggest that elevated serum cardiac troponin I in AC setting is associated with the severity of the disease and with the likelihood of ventricular arrhythmias (74). This has, however, not yet been corroborated in human studies.

7 Therapy

Currently, a specific therapy for AC is not available and therefore management of the disease focuses on slowing its progression and preventing sudden cardiac death. Although some therapies may be more beneficial than others, a combined approach is advised for the maximum benefit. Since AC patients are a diverse group, treatment approach should always be decided on a case-by-case basis.

7.1 Lifestyle changes

Lifestyle changes are necessary when the diagnosis of AC is suspected. Physical exercise has been shown to promote phenotypic expression in AC patients and is a main factor that triggers life-threatening ventricular arrhythmias. Competitive sports have shown a five--fold increase in the risk of sudden death in adolescents and young adults with AC (75,76). Importantly, this is also true for asymptomatic desmosomal mutation carriers where endurance training or frequent exercise has been shown to promote the expression of AC phenotype (77). Therefore, current guidelines recommend that not only affected individuals, but also healthy AC-associated gene mutation carriers refrain from any competitive or endurance sport activity (67).

7.2 β-blocker therapy

Despite the lack of prospective randomized data β-blocker therapy should be considered as an additional antiadrenergic therapy in all patients with confirmed AC regardless of the presence of AC-associated symptoms or arrhythmic manifestation because of its ability to mitigate heart failure symptoms, lower the risk of exercise-induced ventricu-

lar arrhythmias and to slow myocardial disease progression by lowering the RV workload (29,67). Prophylactic use of β-blocker therapy in genotype positive but phenotype negative individuals does not seem justified as there are no studies demonstrating a clear therapeutic benefit for these patients (67).

7.3 Pharmacological antiarrhythmic management

Since the available data is limited to case–control studies, retrospective analyses and clinical registries, decision for antiarrhythmic drug therapy and choice of drug are based on extrapolation from other diseases, personal experience, institutional consensus and individual decisions (67,78,79). In patients that experience frequent premature ventricular beats or ventricular arrhythmias without associated haemodynamic instability, β-blocker or/and class III antiarrhythmic drugs (sotalol, amiodarone) were shown to be the most effective antiarrhythmic agents to reduce arrhythmia burden (3,80,81).

Importantly, in AC patient's antiarrhythmic therapy alone does not efficiently prevent SCD and should therefore always be an adjunct to implantable cardioverter-defibrillator (ICD) and/or to catheter ablation (67).

8 Heart failure management

In AC patients who develop symptomatic heart failure general principles of heart failure management should be applied. Angiotensin-converting-enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARB), β-blockers, aldosterone antagonists, digoxin and/or diuretics should be used as per current AHA/ESC heart failure guidelines (82). The efficiency of heart failure therapy has, unfortunately, not been prospectively validated, but current evidence suggests that applying heart failure therapy in these patients may slow myocardial remodelling and the progression of heart failure. It remains undetermined whether this therapy affects the arrhythmia burden or survival of patients with AC. In the absence of heart failure symptoms, empiric therapy with ACE inhibitors or ARBs may be considered in patients with reduced RV and/or LV systolic function, based on extrapolation from heart failure therapy in other diseases.

8.1 Anticoagulation

An annual incidence of 0.5 % for thromboembolic events in AC patients with severe RV dilatation was reported during a mean follow-up period of 99 ± 64 months (83). If advanced morphological or electrophysiological changes are found in AC patients that may further increase the risk for thromboembolic events, anticoagulation therapy should be considered (67). Specifically, long-term oral anticoagulation is indicated for secondary prevention in patients with documented intracavitary thrombus or venous/systemic thromboembolism (67). Importantly, prophylactic anticoagulation for primary prevention of thromboembolism on the basis of ventricular dilatation/dysfunction, either global or regional, is not recommended (67).

8.2 Non-pharmacological approaches

8.2.1 ICD therapy

Currently randomised trials to guide implantable cardioverter-defibrillator (ICD) therapy in AC patients are lacking for ethical reasons, low disease pre-

valence and low event rates. In general, considering the nature of the disease, the indications for ICD should be reviewed in all patients with AC, however, not all patients with AC will require ICD at the time of diagnosis. The decision for ICD implantation should be the result of a balanced evaluation of the patient's arrhythmic profile and the potential risk for device-related complications. The last ITF Consensus Statement defines 3 categories of risk, based on an estimated annual risk of life-threatening arrhythmic events. The patients in high-risk group (estimated annual event rate > 10 %) should receive ICD therapy. The indication for ICD therapy is less straightforward in intermediate-risk group (estimated annual event rate > 1–10 %) and decision to implant an ICD in this subgroup of AC patients should be made on case-by-case basis. The ICD therapy is generally not recommended in low-risk group (estimated annual event rate < 1 %). The indications for ICD implantation are reviewed in Table 3 (29,67,84).

ICD therapy was shown to be safe and efficient with the estimate survival benefit ranging from 26 % to 50 % during follow-up (85-96). A survival benefit of ICD therapy of 23 %, 32 % and 35 % after 1, 3 and 7 years of follow up, respectively, has recently been documented in high risk patients (88). On the other hand, 62 % of AC patients with ICD had an ICD-associated adverse event, which may be explained by the underlying AC pathophysiology, also affecting the site of RV lead implantation and hindering R-wave sensing (67).

Inappropriate ICD interventions can occur in 10 % to 25 % of patients with AC (96). They are painful and may have a profound clinical and psychological impact on the patients (97). The incidence of inappropriate ICD discharges can be lowered by appropriate ICD programming and administration of antiarrhythmic medication (67,98).

Table 3: Indications for ICD in AC patients. VF – ventricular fibrillation; VT – ventricular tachycardia; RV – right ventricle; LV – left ventricle; (adopted form Corrado et al. (29))

Category of risk	Risk factors	Indication for ICD	Class of recommendation
High risk (>10 %/year)	• VF • Sustained VT • Severe RV/LV dysfunction	Recommended	Class I
Intermediate risk (1–10 %/year)	• Unexplained syncope • Non-sustained VT • Moderate RV/LV dysfunction	Should be considered	Class IIa
	• Genetics status • Male gender • Frequent premature ventricular beats (≥1000/day) • Inducibility at EP study • Extent of negative T-waves • Amount of fibro-fatty scar • Multiple desmosomal-gene mutations	May be considered	Class IIb
Low risk (<1 %/year)	• Healthy gene carriers • Patients with definite AC (no risk factors)	Not recommended	Class III

8.2.2 Catheter ablation

Arrhythmias in AC patients can also be efficiently managed by catheter ablation. With endocardial catheter ablation acute success was achieved in 60 % - 80 % of patients, whereas the recurrences during 3- and 5-year follow-up were as high as 50 % and 70 % respectively. The most likely reason for this is the progressive nature of AC (99,100). If the endocardial approach proves unsuccessful, epicardial approach is recommended. As catheter ablation has not been proven to prevent sudden cardiac death it should never be considered as an alternative to ICD, but rather as a complementary strategy to ICD therapy (the potential exception are patients with a drug refractory, haemodynamically stable monomorphic VT who may benefit from ablation but are otherwise graded low or intermediate risk) (101).

8.2.3 Heart transplantation

In cases where AC patients develop advanced heart failure or uncontrollable ventricular arrhythmias, heart transplantation is currently the gold standard of treatment (3,67). Post-transplant survival rates of AC patients are very good (1-year 94 % and 6-year 88 %) and are above the average heart transplant survival curve.

9 Conclusion

AC is a genetic disease of the myocardium where apoptotic cardiomyocytes are replaced by fibro-fatty tissue. It primarily affects the right ventricle, however in advanced stages of the disease the left ventricle can also commonly be significantly affected.

AC is a challenging diagnosis, especially in early stages of the disease, and should be considered in all patients presenting with palpitations, syncope or sudden cardiac death when other, more common causes of these symptoms are excluded. In patients with suspected AC, evaluation according to the current Task Force Criteria should be applied to achieve optimal diagnostic yield.

Combined pharmacological and non-pharmacological approach is advised for achieving maximum clinical and prognostic benefit in this patient population. Although not all AC patients require ICD, all symptomatic AC patients should be evaluated for ICD implantation, as this is the only treatment approach that has been shown to improve survival in this patient cohort. In patients with AC and advanced heart failure or intractable arrhythmias heart transplantation remains the treatment of choice.

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