

Arrhythmogenic right ventricular cardiomyopathy: From pathophysiology to diagnosis and advances in management

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Abstract

Our understanding of arrhythmogenic right ventricular cardiomyopathy (ARVC) has advanced considerably over the past 30-40 years. This is an inherited cardiomyopathy with complicated genetic inheritance and variable penetrance. Desmosomal dysfunction underlies most cases, and appreciating this pathophysiology has contributed to patient management, particularly with respect to exercise restriction to reduce disease progression. The diagnosis is made according to a series of Task Force Criteria, and subsequent management is guided by expert consensus in the absence of comparative data. ARVC is associated with sudden cardiac death (SCD), particularly in young athletic individuals who unknowingly harbour the condition. Risk stratification is important to guide implantable cardioverter-defibrillator use and reduce SCD. Residual gaps in our understanding, particularly surrounding incomplete penetrance, the underlying pathophysiology and risk stratification, are being targeted by collaborative efforts, large registries, prospective studies and translational research.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy associated with syncope, ventricular arrhythmias (VA) and sudden cardiac death (SCD).¹ Early descriptions of the condition were based on small numbers of severely affected individuals with significant arrhythmic events and heart failure.^{2,3} We now have an increased understanding of the phenotypic breadth of this condition, through systematic diagnostic testing (including deep phenotyping with both imaging and electrical evaluation) coupled with family screening and genetic testing.

Desmosomal dysfunction causes disease in most patients and a pathogenic mutation can be identified in approximately 60% of those affected.^{4,5} Although inheritance is usually autosomal dominant, there is variable penetrance and some affected individuals may demonstrate a mild and even absent phenotype.

Epidemiology

ARVC has an estimated prevalence of 1 in 1000 to 1 in 5000; higher in European countries such as Italy and Germany.⁶ Patients typically present between the second and fifth decade. It is unusual for clinical signs and symptoms to occur younger than 12 or older than 60 years of age.^{5,7} Phenotypic expression is more prevalent in males than females, and male subjects appear more likely to develop severe disease and arrhythmic events.^{8,9} In some cases this sex difference relates to genotype. For example, males carrying the S358L mutation in TMEM43 develop lethal VA at a younger age than their female counterparts.¹⁰

ARVC is an important cause of SCD in the young, particularly in young athletes, where events frequently occur during exercise.^{11,12} Competitive sport is associated with earlier ARVC presentation and an increased risk of fatal arrhythmias.¹³ SCD may occur in the absence of clear phenotype and remote ARVC diagnoses have been made in some sudden unexplained death victims only by family screening and molecular autopsy.¹⁴

Genetics

Inheritance is most commonly autosomal dominant, but incomplete penetrance may obscure Mendelian patterns.¹⁵ ARVC is associated with mutations in genes encoding desmosomal proteins, most commonly plakophilin-2 [PKP2], desmoglein-2 [DSG2], desmoplakin [DSP] and desmocollin-2 [DSC2](Table 1).¹⁶⁻¹⁸ Compound and digenic heterozygosity are frequent and likely contribute to variable penetrance and the complexity of inheritance patterns.¹⁹ Increased penetrance and more severe disease have been associated with multiple mutations.²⁰ Autosomal recessive forms are rare. These include cardiocutaneous syndromes Naxos and Carvajal disease, where cardiomyopathy is found in association with palmoplantar keratoderma and woolly hair.^{21,22} Causal mutations in extra-desmosomal genes have also been described.

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Key words: Arrhythmogenic right ventricular cardiomyopathy; sudden cardiac death; ventricular arrhythmias.

Conflicts of interests: the authors declare no potential conflicts of interests.

Received for publication: 15 August 2017.

Revision received: 10 December 2017.

Accepted for publication: 12 December 2017.

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Cardiogenetics 2017; 7:6995

doi:10.4081/cardiogenetics.2017.6995

These include a Newfoundland founder population with the S358L mutation in TMEM43 which causes a fully penetrant aggressive form of the disease with high incidence of SCD and heart failure.²³

Genotype-phenotype correlations

Patients with multiple mutations have earlier occurrence of ventricular arrhythmias and higher rates of LV dysfunction and cardiac transplantation.²⁴ Heart failure with LV dysfunction is more frequently associated with DSP than PKP2 mutations and LV involvement appears more marked in families with chain terminating mutations.²⁴⁻²⁶ Patients with PKP2 variants may have earlier onset of symptoms and VA.²⁷ Overall, missense mutation carriers appear to have similar outcomes compared with truncating and splice site mutation carriers.²⁴ However, there is significant variation within families.²⁸

Pathophysiology

Histopathology demonstrates patchy lymphocytic infiltrates, myocyte death and fibrofatty replacement of ventricular myocardium starting in the epicardial and midmyocardial layers. This leads to wall thinning and aneurysmal dilatation. The classical pattern of disease affects the right ventricle (RV) with structural changes frequently located in the subtricuspid region,

right ventricular outflow tract (RVOT) and apex.²⁹ This distribution is known as the *triangle of dysplasia*. Non-classical patterns of disease, with biventricular involvement and isolated left ventricular (LV) disease, are increasingly recognised with advances in imaging.³⁰ Renaming the condition arrhythmogenic cardiomyopathy has consequently been suggested.²⁵

Desmosomal dysfunction appears to be the common final pathway for most ARVC cases. Healthy desmosomes reside within the intercalated disc. These desmosomes provide mechanical continuity between myocytes and mediate intracellular and intercellular signal transduction.³¹ Electron microscopy studies have demonstrated remodelling of the intercalated disc and desmosomal loss in myocardial biopsies from ARVC patients.³² Immunohistochemical studies have shown that mutant desmosomal proteins shift from the intercalated disc into the cell cytoplasm and nucleus causing changes in nuclear signalling and gene transcription.³³ Animal studies have suggested that genetically determined desmosomal abnormalities disrupt intercellular junctions, leading to myocyte detachment and eventual loss. Furthermore, increased expression of adipogenic and fibrogenic genes resulting from changes in nuclear signalling and gene transcription contributes to fibrofatty scarring.^{34,35} Mechanical stress appears to worsen desmosomal dysfunction. This may partly explain why adverse outcomes are more common in athletes with ARVC and why exercise accelerates RV dysfunction in mouse models of disease.^{36,37}

Within the intercalated disc, the desmosome interacts with sodium channels (Nav 1.5) and gap junction proteins (connexin 43) to regulate adhesion, excitability and cell-to-cell coupling. This network of proteins is known as the *connexome*.³¹ Ventricular arrhythmias in ARVC appear to result from slowed cardiac conduction creating macro-reentry circuits. This may occur through areas of scar and/or as a result of gap junction remodelling leading to decreased connexin 43 and reduced sodium current.^{38,39} This latter theory may underlie the clinical overlap with the Brugada syndrome observed in some cases.⁴⁰

TMEM43 is a nuclear membrane protein which may form part of an adipogenic pathway.²³ Murine cell studies have shown that the S358L missense mutation alters the localisation of intercalated disc proteins, changes gap junction function and reduces conduction velocity.⁴¹ However, the mechanism by which this pathogenic variant causes ARVC is poorly understood at present.

Clinical presentation and natural history

Symptoms are usually due to VA and include palpitations, lightheadedness, syncope, cardiac arrest and SCD.⁵ SCD is an important, but uncommon, first presentation in some young adults, particularly athletes harbouring the condition.³ In diagnosed and treated ARVC patients, the long-term outcome is favourable with low rates of SCD, cardiac transplantation and cardiac mortality.^{5,24} Different phases are described in ARVC disease progression: the early *concealed* phase where individuals are usually asymptomatic but still at risk from SCD; the overt *electrical* phase where individuals present with arrhythmias but structurally normal hearts by conventional imaging; the *structural* phase where individuals exhibit ventricular morphological abnormalities; and rarely diffuse progressive disease with RV, LV or biventricular heart failure.⁴² Left ventricular involvement was previously thought to develop in the later stages of disease, but the advent of contrast enhanced CMR and genetic testing has shown that in some patients, particularly those with DSP mutations, LV disease occurs early and may be dominant or isolated.^{24,25,30} Electrical changes do appear to pre-date structural disease however. When diagnosing ARVC, abnormal imaging with a completely normal ECG should be considered suspicious and warrants careful review.⁴³

Diagnosis

There is no single gold standard investigation for ARVC. Diagnosis is made according to a series of Task Force criteria (TFC).¹ These comprise data from cardiac imaging, electrocardiography, endomyocardial biopsy (when performed), family history and genetic testing. Categories include major and minor criteria (equivalent to 2 points and 1 point respectively). Patients may be classified as definitely affected, borderline or possibly affected depending on the number of points they accumulate. A definite diagnosis requires four points (Table 2). The original 1994 TFC were based on clinical experience in patients with severe disease.⁴⁴ These were highly specific but lacked sensitivity for the diagnosis of an early phenotype. In addition, qualitative analysis of CMR data resulted in ARVC over-diagnosis.⁴⁵ The TFC were revised in 2010 to improve diagnostic sensitivity, albeit in the absence of a gold-standard. Revised TFC included genetic criteria, new electrical parameters and quantification of cardiac imaging.¹ This led to increased ARVC diagnosis in familial disease and for carriers of desmosomal mutations, but reduced numbers of patients fulfilling CMR criteria, creating a subgroup who no longer satisfied TFC and have subsequently had their ARVC diagnosis removed.⁴⁶ Unfortunately some patients underwent ICD implantation based on historic misinterpretation of CMR studies or overtreatment of benign outflow tract form of ventricular tachycardia.⁴⁷

Table 1. Arrhythmogenic right ventricular cardiomyopathy (ARVC) associated genes.

Genotype	Gene	Locus	Protein	% of disease*
ARVC 1	<i>TGFB3</i>	14q24.3	Transforming growth factor-beta 3	-
ARVC 2	<i>RYR2</i>	1q43	Cardiac ryanodine receptor	-
ARVC 3	<i>Unknown</i>	14q12-q22	-	-
ARVC 4	<i>TTN</i>	2q32.1-q32.3	Titin	-
ARVC 5	<i>TMEM43</i>	3p25.1	Transmembrane protein 43	-
ARVC 6	<i>Unknown</i>	10p14-p12	-	-
ARVC 7	<i>DES</i>	2q35	Desmin	-
ARVC 8	<i>DSP</i>	6p24	Desmoplakin ^o	2%-12%
ARVC 9	<i>PKP2</i>	12p11	Plakophilin-2	25%-40%
ARVC 10	<i>DSG2</i>	18q12.1	Desmoglein-2	5%-10%
ARVC 11	<i>DSC2</i>	18q12.1	Desmocollin-2	2%-7%
ARVC 12	<i>JUP</i>	17q21.2	Plakoglobin [#]	-
Other	<i>PLN</i>	6q22.1	Phospholamban	-
	<i>LMNA</i>	1q22	Lamin A/C	-
	<i>SCN5A</i>	3p21	Cardiac sodium channel	-
	<i>CTNNA3</i>	10q22.2	Alpha-T-catenin	-

*% of disease included where >5%; ^orecessive form: Carvajal syndrome; [#]recessive form: Naxos disease.

Electrocardiographic features and ventricular arrhythmias

Electrocardiographic (ECG) features include repolarization (T-wave inversion; TWI) and depolarization (epsilon waves, terminal activation delay of the QRS complex) abnormalities.⁴⁸ TWI and epsilon waves are associated with diffuse disease and found less commonly in early, localised ARVC.⁴⁸ VA include variable frequency of ventricular ectopy and ventricular tachycardia, which may degenerate into ventricular fibrillation (Figure 1). VA are often triggered by exercise and exercise testing may reveal latent disease.^{3,49} ECG changes are classically seen in the right precordial leads (V_1 - V_3), with extent of changes incorporated into major or minor TFC. Right ventric-

ular related VA have a left bundle branch block (LBBB) morphology, with a variable axis depending on the origin or exit of the arrhythmia. In left dominant disease, ECG changes are found in the inferolateral leads and VA have right bundle branch block morphology.³⁰ Late potentials on signal-averaged ECG are thought to represent depolarization abnormalities secondary to slowed conduction, due to myocardial scar. Although late potentials are associated with other myocardial pathologies, these have high diagnostic sensitivity and specificity when ARVC patients are compared with controls.⁵⁰

Cardiac imaging

CMR is the preferred diagnostic imaging

technique.⁴³ It is the gold standard for cardiac volume and function assessment. Tissue characterisation, including late gadolinium enhancement (LGE) provides incremental information regarding myocardial fibrofatty scar.⁵¹ Echocardiography allows longitudinal assessment of ventricular function, particularly for patients with implantable-cardioverter defibrillators (ICD) *in situ*, where CMR may be contraindicated (Figure 2). Original TFC for imaging, including myocardial fatty infiltration, were qualitative and resulted in over-diagnosis.^{44,45} When the TFC were revised, imaging parameters were quantified and CMR assessment of myocardial fat was no longer recommended (Table 2).¹ Classical disease causes RV regional wall motion abnormalities (RWMA) with

Table 2. Revised 2010 Task Force Criteria (TFC) for arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis.

	Major criteria	Minor criteria
Global or regional dysfunction and structural alterations	<p><i>2D echo</i>: Regional RV akinesia, dyskinesia or aneurysm and 1 of the following (end diastole):</p> <ul style="list-style-type: none"> - PLAX RVOT ≥ 32mm (≥ 19 mm/m²) - PSAX RVOT ≥ 36mm (≥ 21 mm/m²) - Fractional area change $\leq 33\%$ <p><i>MRI</i>: Regional RV akinesia or dyssynchronous RV contraction and 1 of the following:</p> <ul style="list-style-type: none"> - RV end-diastolic volume ≥ 110 ml/m² (male) or ≥ 100ml/m² (female) <p><i>RV angiography</i>:</p> <ul style="list-style-type: none"> - Regional RV akinesia, dyskinesia or aneurysm 	<p><i>2D echo</i>: Regional RV akinesia, dyskinesia or aneurysm and 1 of the following (end diastole):</p> <ul style="list-style-type: none"> - PLAX RVOT ≥ 29 to < 32mm (≥ 16 to < 19 mm/m²) - PSAX RVOT ≥ 32 to < 36mm (≥ 18 to < 21 mm/m²) - Fractional area change $> 33\%$ to $\leq 40\%$ <p><i>MRI</i>: Regional RV akinesia or dyssynchronous RV contraction and 1 of the following:</p> <ul style="list-style-type: none"> - RV end-diastolic volume ≥ 100 to < 110 ml/m² (male) or ≥ 90 to < 100 ml/m² (female)
Tissue characterization of 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 60% if estimated) with fibrous replacement of the RV free wall myocardium in ≥ 1 sample with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	<p><i>ECG</i>:</p> <ul style="list-style-type: none"> - Inverted T waves in right precordial leads (V_1-V_3) or beyond in individuals > 14 years of age (in the absence of complete RBBB with QRS ≥ 120ms) 	<p><i>ECG</i>:</p> <ul style="list-style-type: none"> - Inverted T waves in leads V_1-V_2 in individuals > 14 years of age (in the absence of complete RBBB) or in leads V_4, V_5, V_6 - Inverted T waves in leads V_1-V_4 in individuals > 14 years of age in the presence of complete RBBB
Depolarization/conduction abnormalities	<p><i>ECG</i>: Epsilon wave (reproducible low-amplitude signals between end of QRS complex to beginning of T wave) in leads V_1, V_2 or V_3</p>	<p><i>SAECG</i>: late potentials in ≥ 1 of 3 parameters in the absence of QRS duration ≥ 110ms on ECG:</p> <ul style="list-style-type: none"> - Filtered QRS duration ≥ 114ms - Duration of terminal QRS < 40 μV ≥ 38 ms - Root-mean-square voltage of terminal 40 ms ≤ 20 μV <p><i>ECG</i>: Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS (including R') in leads V_1, V_2 or V_3 in the absence of complete RBBB</p>
Arrhythmias	VT of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III and aVF and positive in aVL)	RVOT configuration VT of LBBB morphology with inferior axis (positive QRS in leads II, III and aVF and negative in aVL) or unknown axis <i>Holter</i> : > 500 ventricular ectopics/24 hours
Family history	ARVC confirmed in a first-degree relative who meets current TFC ARVC confirmed pathologically at autopsy or surgery in a first-degree relative Identification of a pathogenic mutation* categorized as associated or probably associated with ARVC in the patient under evaluation	ARVC in a first-degree relative in whom it is not possible to determine whether the family member meets current TFC Premature sudden death (< 35 years of age) due to suspected ARVC in a first-degree relative ARVC confirmed pathologically or by current TFC in a second-degree relative

PLAX parasternal long-axis view; RVOT, right ventricular outflow tract; PSAX, parasternal short-axis view; RBBB, right bundle branch block; VT, ventricular tachycardia. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories. *A pathogenic mutation is a DNA alteration associated with ARVC that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. Adapted from Marcus *et al.*, 2010.¹

Sudden death risk

Increased risk of SCD appears to be associated with male gender, proband status, unexplained cardiac syncope, competitive and endurance exercise, extensive structural disease, electrical instability (VA and/or frequent ventricular ectopy) and multiple pathogenic variants or a mutation in *TMEM43*.^{13,20,23,24,62-66} The prognostic value of programmed ventricular stimulation in asymptomatic patients with ARVC remains unclear, but invasive evaluation of myocardial scar and fragmented, delayed electrograms may provide incremental information regarding SCD risk.^{63,64,67}

ICD therapy reduces SCD in high-risk patients with ARVC, but ICD implantation carries risks of complication, particularly lead-related adverse events and inappropriate shocks in younger patients.^{64,68,69} Therefore, accurate risk stratification and appropriate patient selection is important. Newer subcutaneous ICD (S-ICD) technology represents progress towards a less invasive approach in selected patients without pacing indications. This appears safe and efficacious and may reduce complications related to transvenous leads. Not all patients are suitable however, and must be carefully screened. In addition inappropriate shock rates remain high and performance data is limited at present.⁷⁰

Management

Patient management involves measures to decrease symptoms and disease progression, to protect against SCD and to organise family screening. Data regarding patient management and risk stratification in ARVC come from single centre reports and small multicentre registries.⁷¹ Patients with ARVC should be evaluated every 1-2 years.

Measures to decrease symptoms and reduce ICD therapies

Antiarrhythmic drug therapy may improve quality of life by reducing symptomatic VA. Beta-blockers, sotalol and amiodarone are used. A combination of amiodarone with a beta-blocker appears most effective, but cumulative side effects limit long-term use of amiodarone in young patients.⁷² In patients with sustained monomorphic VT, invasive electrophysiological voltage mapping can identify areas of scar and guide catheter ablation of VA. This is more successful when epicardial and endocardial approaches are combined (Figure 4).⁷³ Due to the progressive nature of disease, there may be recurrences but recent data suggests good outcomes, particularly reduction in long-term amiodarone

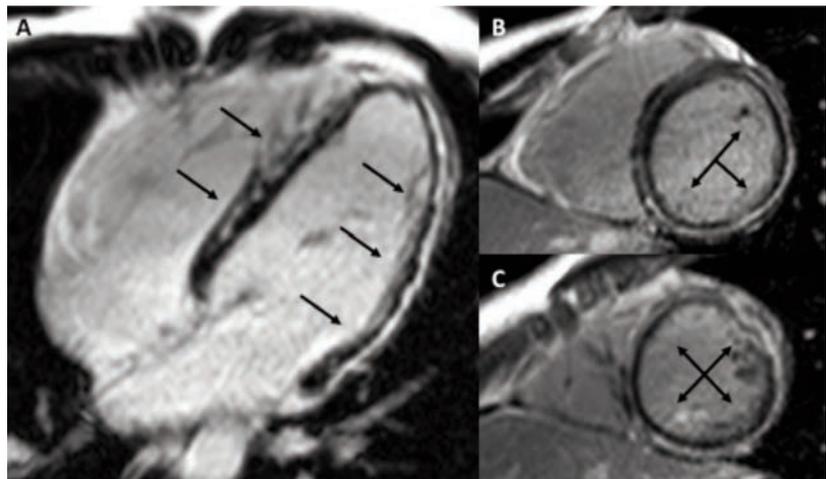


Figure 3. Cardiac magnetic resonance (CMR) imaging demonstrates subepicardial and midmyocardial left ventricular late gadolinium enhancement in a patient with arrhythmogenic right ventricular cardiomyopathy (ARVC). Panel (A) is a long axis four chamber image and panels (B) and (C) are short axis views.

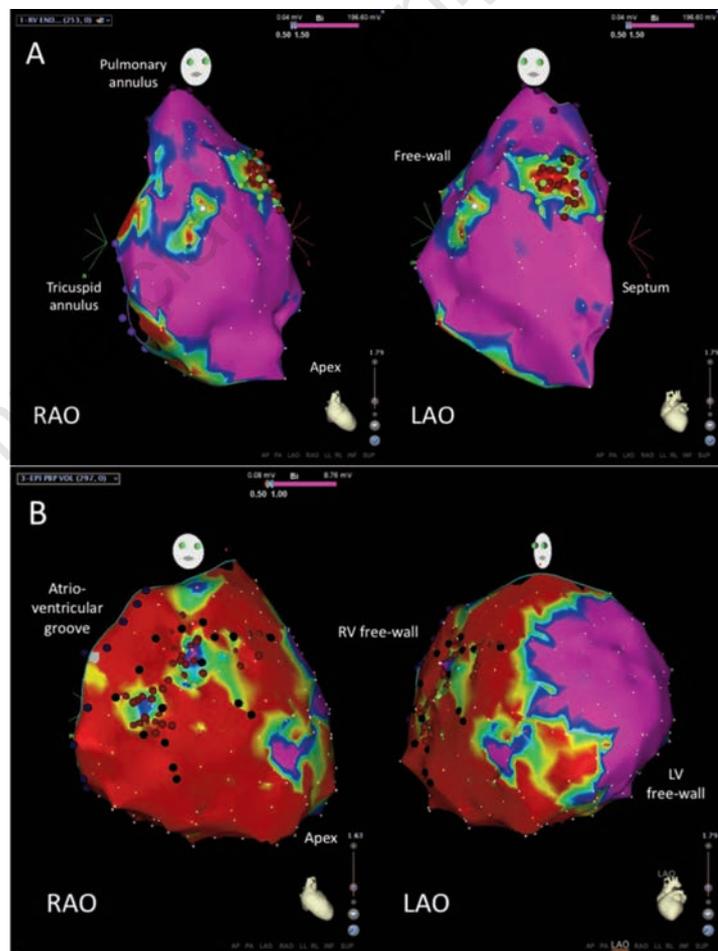


Figure 4. Endocardial and epicardial voltage mapping. Panel (A) shows right ventricular endocardial bipolar voltage maps in the right anterior oblique (RAO) and left anterior oblique (LAO) views from a 22-year-old patient with arrhythmogenic right ventricular cardiomyopathy (ARVC) and ventricular tachycardia refractory to amiodarone. Panel (B) shows epicardial bipolar voltage maps from the same views. Purple reflects healthy myocardium and red reflects severely scarred myocardium or epicardial fat. Note the patchy endocardial scar but more extensive epicardial scar. The black or green markers indicate late potentials (delayed electrical activity within the scar). The red markers are ablation lesions performed during the procedure.

Table 3. Risk stratification and indications for implantable-cardioverter defibrillator (ICD) therapy.

Risk of serious arrhythmia	Markers of risk	ICD guidance
High risk (>10% per year)	- Aborted SCD - Sustained VT - Severe RV and/or LV dysfunction (RV FAC \leq 17%, RVEF and/or LVEF \leq 35%)	ICD indicated (class I)
Intermediate risk	\geq 1 major risk factor - Syncope - Non-sustained VT - Moderate RV and/or LV dysfunction (RV FAC 17%-24%, RVEF 36%-40% and/or LVEF 36%-45%)	ICD should be considered (class IIa)
Intermediate risk	\geq 1 other (minor) risk factor	ICD may be considered (class IIb)
Low risk (<1% per year)	No risk factors Healthy gene carriers	ICD not indicated (class III)

SCD, sudden cardiac death; VT, ventricular tachycardia; RV, right ventricle; LV, left ventricle; FAC, fractional area change; RVEF, RV ejection fraction; LVEF, LV ejection fraction. Adapted from Corrado *et al.* 2015.⁷¹

therapy.^{74,75} Heart failure (RV or LV) is treated with standard pharmacologic therapy including angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers, beta-blockers and diuretics.⁷¹ Cardiac transplantation may be considered in severe disease.⁷⁶ Anticoagulation is indicated for patients who develop intracardiac thrombus and/or systemic thromboembolism.⁷¹

Measures to decrease disease progression

Endurance training at a competitive level has been shown to exacerbate the ARVC phenotype and therefore avoidance of high-level endurance training and competitive sports is recommended. Engagement in recreational sports with low cardiovascular demand appears acceptable.⁷⁷

Reduction of SCD risk

Patients with aborted SCD and sustained VT with haemodynamic compromise are at highest risk of SCD (up to 10% per annum) and ICD insertion is recommended.⁷⁸ Consensus guidelines based on extrapolation from other cardiomyopathies and personal experience also include severe ventricular dysfunction as a high-risk feature (RVEF and/or LVEF \leq 35%).⁷¹ ICD therapy may be considered in patients with major risk factors including unexplained syncope, non-sustained VT and moderate RV and/or LV dysfunction. It is generally agreed that asymptomatic patients without risk factors and healthy gene carriers are at low risk of arrhythmic events and do not require ICD insertion (Table 3).^{71,78} In borderline patients, an implantable cardiac monitor may be considered to assess for VA and aid decisions about subsequent ICD placement.

Family screening and identification of subtle disease

Family screening comprises clinical and genetic evaluation. Clinical testing comprises ECG, echocardiography and/or CMR, Holter monitoring and exercise testing, with interpretation of results guided by the modified TFC (for familial disease).^{1,71} Definitive genetic diagnosis in an index case enables cascade screening of family members. Those who test positive continue clinical follow-up whereas those who test negative may be discharged. However, given the complexities of ARVC genetics and the uncertainty surrounding pathogenicity of some variants, caution should be exercised prior to discharge of gene-negative relatives.¹⁶ Family members and healthy gene carriers should be evaluated every 2-3 years.⁷¹

Future directions

In a rare disease without randomised controlled trial data, the evidence base for guidelines is limited. There are unanswered questions, particularly surrounding variable penetrance, the underlying pathophysiology and risk stratification. Collaborative registries will help to address this.⁷⁹ Prospective and multicentre randomised controlled studies with larger patient cohorts and longer follow-up are also needed. Therapeutic advances will depend on improved understanding of the underlying genetic and molecular mechanisms and translational work bringing together basic scientists and clinicians will be important to further advancement in this area.

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