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MYOCARDIAL DISEASE

Arrhythmogenic right ventricular cardiomyopathy: an update

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease that predominantly affects the right ventricle (RV). The main pathologic feature is the progressive loss of RV myocardium and its replacement by fibrofatty tissue. The condition was initially believed to be a developmental defect of the RV myocardium, leading to the original designation of “dysplasia”. This concept has evolved over the last 25 years into the current perspective of a genetically determined “cardiomyopathy”. The estimated prevalence of ARVC in the general population ranges from 1 in 2000 to 1 in 5000. A familial background has been demonstrated in 30–50% of ARVC cases. Clinical manifestations develop most often between the second and third decade of life and are related to ventricular tachycardia (VT) or ventricular fibrillation (VF) which may lead to sudden death, mostly in young people. Later in the disease evolution, progression of RV muscle disease and left ventricular (LV) involvement may result in right or biventricular heart failure. Ventricular arrhythmias are worse during or immediately after exercise, and participation in competitive athletics has been associated with an increased risk for sudden death. Clinical diagnosis of ARVC is often difficult due to the non-specific nature of disease features and the broad spectrum of phenotypic manifestation, ranging from severe to concealed forms. Early detection and preventive therapy of young individuals at highest risk of experiencing sudden cardiac death may modify the natural history of the disease.

In 2000 we published in the *Education in Heart* series a comprehensive review of the diagnosis, prognosis and treatment of ARVC.¹ Since this publication, advances in the genetic background, epidemiology, clinical diagnosis, imaging, and treatment have provided significant new insights into the management of ARVC patients.² This article offers an up-to-date perspective on molecular genetics, clinical and imaging diagnosis, risk stratification and therapeutic strategies for prevention of sudden death in ARVC.

DIAGNOSIS

Genetics and preclinical diagnosis

The discovery of gene mutations involved in the pathogenesis of ARVC has offered the potential to identify genetically affected individuals by DNA characterisation before the disease phenotype occurs. Clinical impact of genotype determination

includes early diagnosis with prediction of phenotype, arrhythmic risk stratification and therapeutic interventions aimed to prevent sudden death.³

Genetic background

The inherited nature of ARVC has been recognised since 1982 when Marcus *et al* described 24 adult cases, two in the same family. In 1988 a report on eight Italian families suggested the autosomal dominant pattern of inheritance with incomplete penetrance and variable expression. ARVC affects men more frequently than women, with an approximate ratio of 3:1. The first chromosomal locus (14q23-q24) for autosomal dominant ARVC was published in 1994 after clinical evaluation of a large Venetian family. Subsequently, linkage analysis provided evidence for genetic heterogeneity with sequential discovery of several ARVC loci on chromosomes 1, 2, 3, 6, 10, 12, 14, and 18 (table 1). An autosomal recessive variant (so-called Naxos disease) in which there is a co-segregation of cardiac (ARVC), skin (palmoplantar keratosis) and hair (woolly hair) abnormalities has been mapped on chromosome 17 (locus 17q21).

The first disease-causing gene, the JUP gene, was identified by McKoy *et al* in patients with Naxos disease.⁴ The JUP gene encodes desmosomal protein plakoglobin, which is the major constituent of cell adhesion junction. Its discovery suggested that ARVC is a cell-to-cell junction disorder and stimulated research for other related genes. Mutations in desmosomal protein genes have also been shown to cause the more common (non-syndromic) autosomal dominant form of the disease (table 1). Desmoplakin (DSP) was the first defective gene to be associated with autosomal dominant ARVC by Rampazzo *et al*.⁵ Subsequently, a variety of mutations in plakophilin-2 (PKP2) have been identified in almost one third of unrelated probands from three different cohorts of ARVC patients across the world.⁶ Recent studies showed mutations in two additional desmosomal genes—desmoglein-2 (DSG-2) and desmocollin-2 (DSC-2) genes—in familial cases of ARVC.^{7–9} A non-syndromic form of ARVC caused by a dominant JUP gene mutation has been also reported.

Autosomal dominant ARVC has been linked to other genes unrelated to cell adhesion complex (table 1), such as the gene encoding for cardiac ryanodine receptor (RyR2), which is responsible for calcium release from the sarcoplasmic reticulum,

Table 1 Chromosomal loci and disease-causing genes in arrhythmogenic right ventricular cardiomyopathy

Designation (pattern of inheritance)	Chromosomal locus	Gene mutations
ARVD1 (AD)	14q23-q24	Transforming growth factor- β 3 (TGF β 3)
ARVD2 (AD)	1q42-q43	Cardiac ryanodine receptor (RyR2)
ARVD3 (AD)	14q12-q22	?
ARVD4 (AD)	2q32.1-q32.3	?
ARVD5 (AD)	3p23	Transmembrane 43 (TMEM43)
ARVD6 (AD)	10p12-p14	?
ARVD7 (AD)	10q22	?
Naxos disease (AR)	17q21	Plakoglobin (JUP)
ARVD8 (AD)	6p24	Desmoplakin (DSP)
ARVD 9 (AD)	12p11	Plakophilin-2 (PKP2)
ARVD 10 (AD)	18q12.1	Desmoglein-2 (DSG2)
ARVD 11 (AD)	18q12.1	Desmocollin-2 (DSC2)
ARVD 12 (AD)	17q21	Plakoglobin (JUP)

AD, autosomal dominant; AR, autosomal recessive.

and the transforming growth factor β -3 gene (TGF β 3) which regulates the production of extracellular matrix components and modulates expression of genes encoding desmosomal proteins. The most recently discovered ARVC gene is TMEM43 which causes a highly lethal and fully penetrant disease variant (ARVD5). Little is known about the function of the TMEM43 gene, which may be part of an adipogenic pathway regulated by PPAR γ , whose dysregulation may explain the fibrofatty replacement of the myocardium in ARVC.

Disease pathogenesis

Desmosomes are specialised structures which provide mechanical attachment between cells. In addition, desmosomes are emerging as mediators of intra- and intercellular signal transduction pathways. Proteins from three separate families assemble to form desmosomes: the desmosomal cadherins, armadillo proteins, and plakins (fig 1).

According to the widely accepted “defective desmosome” hypothesis, genetically determined disruption of desmosomal integrity is the key factor in the development of ARVC.¹⁰ It is believed that the lack of the protein or the incorporation of mutant protein into cardiac desmosomes may provoke detachment of myocytes at the intercalated discs, particularly under conditions of mechanical stress (like that occurring during competitive sports activity). As a consequence, there is progressive myocyte degeneration and death with subsequent repair by fibrofatty replacement. Life threatening ventricular arrhythmias may occur either during the “hot phase” of myocyte death as abrupt VF or later in the form of scar related macro-reentrant VT.

Recent data from Garcia-Gras *et al*¹¹ on desmoplakin deficient mice suggest an alternative molecular mechanism which implicates inhibition of the canonical Wnt/ β -catenin signalling through Tcf/Lef transcription factors in the pathogenesis of ARVC. In this study, cardiac specific loss of the desmosomal protein desmoplakin was sufficient to cause nuclear translocation of plakoglobin,

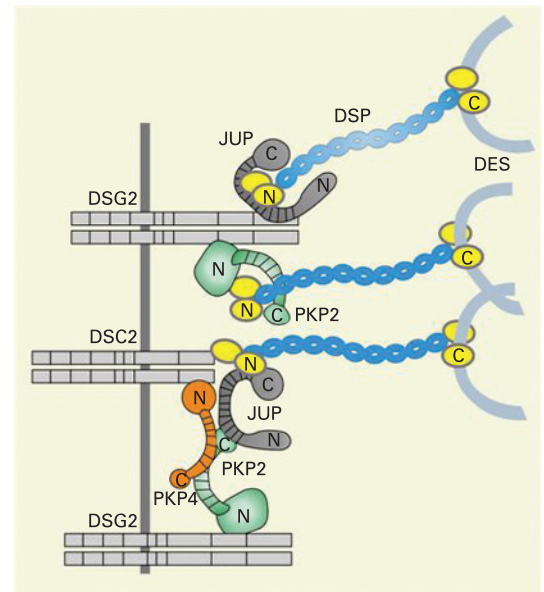


Figure 1 Schematic representation of components of desmosomes which are specialised cell-to-cell adhesion structures found in tissues subjected to mechanical stress, such as skin and heart. There are three major groups of desmosomal proteins: (1) transmembrane proteins (desmosomal cadherins) including desmocollins (DSC) and desmogleins (DSG); (2) desmoplakin (DSP), a plakin family protein that binds directly to intermediate filaments—that is, desmin (DES) in the heart; and (3) linker proteins (armadillo family proteins) including plakoglobin (JUP) and plakophilins (PKP) which mediate interactions between the desmosomal cadherin tails and desmoplakin. Reproduced from Marcus *et al*,² with permission of the publisher.

increased expression of adipogenic and fibrogenic genes, and the development of an ARVC-like phenotype consisting of myocardial fibrofatty infiltration, cavity enlargement and ventricular arrhythmias. This evidence for potential Wnt/ β -catenin signalling defects implicates a role for cell adhesion proteins not only as passive players in providing mechanical attachment between cells, but as regulators in cardiac development, in myocyte differentiation, and in the maintenance of the myocardial architecture.

Clinical impact of genotyping

Clinical manifestations of ARVC usually develop during adolescence and young adulthood, and are preceded by a long “preclinical” phase. Cardiac arrest often occurs in young adults and competitive athletes as the first clinical sign of the disease. The most important clinical impact of genotyping families with ARVC is the possibility to identify genetically affected relatives before a malignant clinical phenotype manifests. This opportunity has significant implications for primary prevention of sudden death itself. Our experience in an ARVC referral centre (University of Padua Medical School) during the past decade showed the favourable clinical outcome (0.08 annual mortality rate) of a large cohort of patients diagnosed with

familial ARVC who underwent close follow-up and treatment. Timely therapy with β -blockers and/or implantable cardioverter-defibrillator (ICD) is highly effective in prevention of sudden death in ARVC. This underlines the importance of early ARVC diagnosis by molecular genetic analysis in order to establish a focused prevention strategy based on lifestyle modifications (restriction from competitive sport), family planning, clinical follow-up (recognition of alarming symptoms, detection of ECG/echocardiographic abnormalities and ventricular arrhythmias) and prophylactic therapy (β -blockers, amiodarone, and ICD) to prevent sudden death.³

ECG screening and pre-symptomatic diagnosis

Identification of ARVC by pre-participation screening in still asymptomatic young competitive athletes is a lifesaving strategy. For more than 25 years a systematic pre-participation screening, based on 12 lead ECG in addition to history and physical examination, has been the practice in Italy. A recent study reported the results of a time trend analysis of the changes in incidence rates and causes of sudden cardiovascular death in young competitive athletes age 12–35 years in the Veneto region of Italy between 1979 and 2004, before and after introduction of systematic pre-participation screening.¹² Over the same time interval, a parallel study which examined trends in cardiovascular causes of disqualification from competitive sports in 42 386 athletes undergoing pre-participation screening at the Center for Sports Medicine in Padua was carried out. The annual incidence of sudden cardiovascular death in athletes decreased approximately by 90%, from 3.6/100 000 person-years in the pre-screening period to 0.4/100 000 person-years in the late screening period, whereas the incidence of sudden death among the unscreened non-athletic population did not change significantly over that time. Most of the reduced death rate was due to fewer cases of sudden death from either hypertrophic cardiomyopathy or ARVC. Time trend analysis showed that the incidence of sudden death from ARVC fell by 84% over the 24 year span. This decline in mortality from ARVC paralleled the concomitant increase in the number of affected athletes who were identified and disqualified from competitive sports over the screening periods.

Task force criteria and clinical diagnosis

Standardised diagnostic criteria have been proposed by an International Task Force of the European Society of Cardiology and the International Society and Federation of Cardiology (table 2). The purpose of the task force was to provide diagnostic guidelines to help overcome several problems with specificity of the ECG abnormalities, different potential aetiologies of ventricular arrhythmias with a left bundle branch block morphology, assessment of the RV structure and function, and interpretation of endomyocardial

biopsy findings. The strategy consists of achieving clinical diagnosis by combining multiple sources of diagnostic information, such as genetic, electrocardiographic, arrhythmic, morphofunctional, and histopathologic findings.

Since their publication in 1994, the task force criteria have been extremely useful in providing a standardised approach to the clinical diagnosis of ARVC. The criteria were initially designed to guarantee an adequate specificity for ARVC among index cases with overt clinical manifestations. Task force guidelines have actually helped cardiologists to avoid misdiagnosis of ARVC in patients with dilated cardiomyopathy or idiopathic right ventricular outflow tract tachycardia. However, the diagnostic criteria have been shown to lack sensitivity for identification of early/minor phenotypes, particularly in the setting of familial ARVC. Hence, a revision of such diagnostic guidelines has been proposed with the aim to make a proper diagnosis in first degree relatives with incomplete phenotypic expression.¹³ According to modified criteria, the presence of any one of right precordial T wave inversion, late potentials on signal averaged ECG, a left bundle branch block pattern VT, premature ventricular beats ≥ 200 over 24 h or mild morphofunctional RV abnormalities is considered to be itself diagnostic, in the setting of family screening of probands with clinically or pathologically proven ARVC. Indeed, the chance that such isolated ECG, arrhythmic, or echocardiographic features represent a clinical manifestation of ARVC is definitively higher in family members who have a 50% probability of defective gene transmission.

A further limitation of current task force criteria is the lack of quantitative cut-off values for proper grading of RV dilatation/dysfunction and fibrofatty myocardial replacement.¹⁴ Besides a visual evaluation of RV wall motion and structural abnormalities, a quantitative assessment including measurements of end-diastolic cavity dimensions (inlet, outlet, and mean RV ventricular body), wall thickness, volume and function, either global or regional, is mandatory to enhance the diagnostic accuracy. Revised guidelines for ARVC diagnosis should provide quantitative imaging and histopathologic measurement cut points for defining a normal RV and categorise the various degree of morphofunctional RV abnormalities.

Imaging diagnosis

Contrast ventriculography, echocardiography and cardiac magnetic resonance (MR) are the standard imaging techniques for diagnosing ARVC.^{1 2} Relevant structural abnormalities include global or segmental RV dilatation with or without ejection fraction reduction; wall motion abnormalities, such as ipo-akinesia and dyskinesia (aneurysms and bulgings); and LV involvement. RV angiography is an invasive tool which is usually regarded as the “gold standard” for diagnosis. Echocardiography is a non-invasive and widely used technique which represents the first line

Table 2 Task force criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC)*

Group	Major	Minor
1. Global and/or regional dysfunction and structural alterations	Severe dilatation and reduction of RV ejection fraction with no (or only mild) left ventricular involvement Localised RV aneurysms (akinetic or dyskinetic areas with diastolic bulgings) Severe segmental dilatation of the RV	Mild global RV dilatation and or ejection fraction reduction with normal LV Mild segmental dilatation of the RV Regional RV hypokinesia
2. Tissue characteristics of walls	Fibrofatty replacement of myocardium on endomyocardial biopsy	
3. ECG depolarisation/conduction abnormalities	Epsilon waves or localised prolongation (≥ 110 ms) of the QRS complex in the right precordial leads (V1–V3)	Late potentials seen on signal averaged ECG
4. ECG repolarisation abnormalities		Inverted T waves in right precordial leads (V2 and V3) in people >12 years and in the absence of right bundle branch block
5. Arrhythmias		Sustained or non-sustained left bundle branch block type ventricular tachycardia documented on the ECG, Holter monitoring or during exercise testing Frequent ventricular extrasystoles (more than 1000/24 h on Holter monitoring)
6. Family history	Familial disease confirmed at necropsy or surgery	Family history of premature sudden death (<35 years) due to suspected ARVC Family history (clinical diagnosis based on present criteria)

LV, left ventricle; RV, right ventricle.

*Diagnosis of ARVC in probands is made when two major criteria or one major plus two minor or four minor criteria from different groups are met. According to the proposed revision, the diagnosis of probable ARVC in a first degree family member would be fulfilled by the presence of a single minor criteria from group 1, 3, 4 and 5.

imaging approach for evaluating patients with suspected ARVC or screening family members; moreover, it represents the best modality for assessing disease progression during the follow-up by serial examinations. Both imaging techniques appear to be accurate in detecting overt disease, but they are less sensitive in detecting subtle RV structural and functional abnormalities of early/minor forms of ARVC.

Cardiac MR allows an accurate quantitative RV volume analysis. However, it has been implicated in overdiagnosis of ARVC based on the low specificity of qualitative findings such as increased intramyocardial fat and wall thinning. Moreover, significant interobserver variability in the interpretation of segmental contraction analysis of the RV free wall has been reported. A cardiac MR study demonstrated a 93.1% prevalence of RV wall motion abnormalities in normal subjects, including areas of apparent dyskinesia (75.9%) and bulging (27.6%). All these data indicate that conventional cardiac MR may lead to misdiagnosis of ARVC by showing equivocal morphofunctional RV abnormalities.

The most significant advance in the imaging of ARVC has been the introduction of two techniques for specific detection of the hallmark pathological lesion of ARVC—that is, the loss of the myocardium with fibrofatty replacement.

Late enhancement

Emerging data suggest a key role for late gadolinium enhancement in detection of myocardial fibrofatty scar in both the RV and LV. Tandri *et al*¹⁵ first reported on the clinical role of contrast enhanced cardiac MR. RV delayed enhancement was observed in 67% of patients with ARVC and

correlated with inducibility of sustained monomorphic VT at electrophysiological testing and demonstration of fibrofatty myocardial changes at endomyocardial biopsy. Subsequently, Sen-Chowdhry *et al*¹⁶ demonstrated that LV late enhancement is a common finding in patients with ARVC and provides higher diagnostic sensitivity and specificity than RV late enhancement. In ARVC patients, LV late enhancement predominantly involves the inferolateral and inferoseptal regions, and, unlike subendocardial distribution of ischaemic scar, is characteristically localised in the subepicardial or mid wall layers, similarly to the

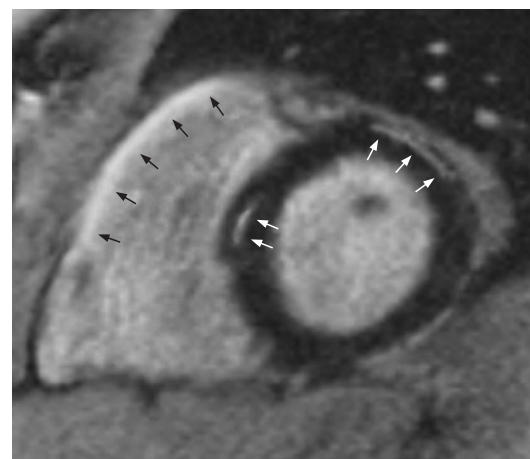


Figure 2 Short axis image after gadolinium injection in a patient with arrhythmogenic right ventricular cardiomyopathy with biventricular involvement. The image shows delayed hyperenhancement on the anteroinfundibular wall of the right ventricle (black arrows), as well as on the interventricular septum and the free wall of the left ventricle (white arrows).

histologic pattern of fibrofatty myocardial replacement found at postmortem examination (fig 2). Prominent LV late enhancement with ventricular dilatation/dysfunction and no or mild RV involvement may be observed in the “left dominant” form of ARVC, which is characteristically related to desmoplakin gene defects. Other clinical markers of this disease variant include ECG abnormalities suggesting LV involvement, such as T wave inversion in the leads exploring the LV (V5, V6, I and aVL), and ventricular arrhythmias of LV origin with a right bundle branch block morphology. The frequent and early finding of LV involvement in ARVC, and the identification of a predominantly left sided variant of the disease, led to the evolving concept that ARVC is a genetically determined heart muscle disease extending across the entire heart (fig 3).

Voltage mapping

Endocardial voltage mapping has the ability to identify areas of myocardial atrophy and fibrofatty substitution by recording and spatially associating low amplitude electrograms to generate a three dimensional electroanatomic map of the RV chamber. The technique has the potential to identify accurately the presence, location and extent of the pathologic substrate of ARVC by demonstration of RV low voltage regions—that is, electroanatomic scars. In ARVC patients, RV electroanatomic scars have been demonstrated to correspond to areas of myocardial depletion and correlate with the histopathologic finding of myocardial atrophy and fibrofatty replacement at endomyocardial biopsy¹⁷ (fig 4).

Demonstration of electroanatomic scar regions by voltage mapping enhances the accuracy of diagnosing ARVC by distinguishing between pure genetically determined myocardial dystrophy and acquired RV inflammatory cardiomyopathy mimicking ARVC.¹³ Moreover, by assessing the electrical (rather than the mechanical) consequences of loss of RV myocardium, voltage mapping may obviate limitations in RV wall motion analysis by traditional imaging techniques such as echocardiography and angiography, and may increase sensitivity for detecting otherwise concealed ARVC myocardial lesions. A recent study showed that electroanatomic voltage mapping may help in the differential diagnosis between idiopathic RV outflow tract tachycardia and the early/minor form of ARVC.¹⁸ Among patients presenting with idiopathic RV outflow tract tachycardia and an apparently normal heart at conventional imaging, RV mapping allowed the identification of those with segmental electroanatomic scars in the RV outflow tract, a finding that correlated with fibrofatty myocardial replacement at endomyocardial biopsy and predisposed to sudden arrhythmic death during follow-up.

Ventricular tachycardia in ARVC is the result of a scar related macro-reentry circuit, similar to that observed in the post-myocardial infarction setting. RV voltage mapping guided catheter ablation has

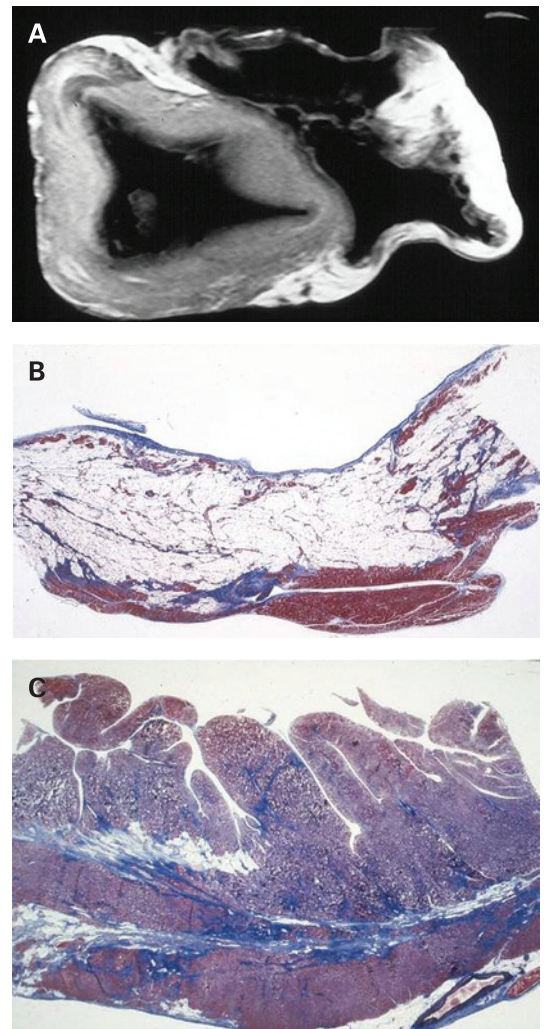


Figure 3 A 35-year-old man who died suddenly with an in vivo diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) with biventricular involvement belonging to a family found positive at genetic screening for desmoplakin mutation. (A) In vitro spin echo cardiac magnetic resonance, short axis cut, shows biventricular dilatation, transmural fatty infiltration of the right ventricular (RV) free wall, and spots of fatty tissue in the posterolateral left ventricular (LV) free wall. (B) Panoramic histologic section of the RV free wall: transmural fibrofatty replacement of the myocardium (Heidenhain trichrome). (C) Panoramic histologic section of the LV lateral wall: fibrofatty with prevalent fibrous tissue replacement is evident in the subepicardial and mid mural layers (Heidenhain trichrome). Reproduced from Marcus *et al*,² with permission of the publisher.

been proposed as a successful therapeutic strategy for VT in ARVC.¹⁹ Voltage mapping is used to identify RV low voltage regions and allows substrate based linear ablation lesions connecting or encircling electroanatomic scars to be created, which result in the interruption of the reentry circuit.

PROGNOSIS AND TREATMENT

Risk stratification

The clinical outcome of patients with ARVC is related to the ventricular electrical instability

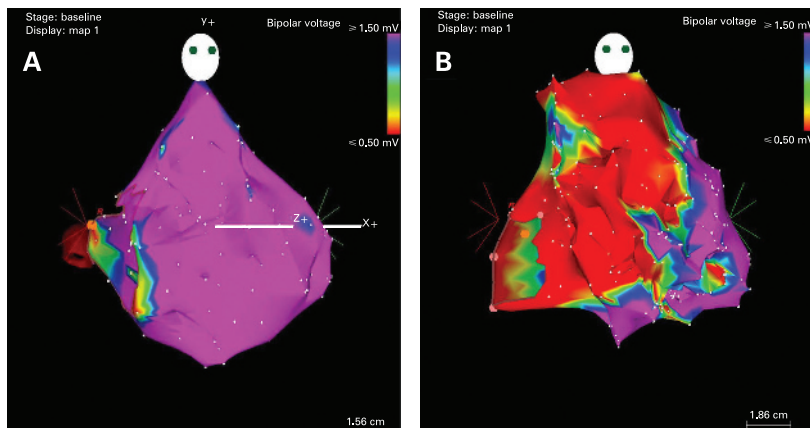


Figure 4 Representative normal and abnormal three dimensional electroanatomic voltage maps. Voltages are colour coded according to corresponding colour bars. Colour range is identical for all subsequent figures: purple represents signal amplitudes >1.5 mV ("electroanatomic normal myocardium"); red <0.5 mV ("electroanatomic scar tissue"); and range between purple and red 0.5 to 1.5 mV ("electroanatomic border zone"). (A) Anteroposterior view of the right ventricular (RV) bipolar voltage map from one control subject entirely represented by normal bipolar voltages. (B) Anteroposterior view of the RV bipolar voltage map from a patient with arrhythmogenic right ventricular cardiomyopathy showing diffuse low amplitude electrical activity involving anterior, lateral, inferobasal, anteroapical and infundibular regions. Reproduced from Marcus *et al*,² with permission of the publisher.

which can precipitate life threatening ventricular arrhythmias at any time during the disease course, and to progressive myocardial loss that may induce ventricular dysfunction and heart failure.^{1 2} The available data suggest that young age, prior cardiac arrest, fast and poorly tolerated VT with different morphologies, syncope, severe RV dysfunction, heart failure with LV involvement, and familial occurrence of juvenile sudden death are the major determinants in predicting sudden death and worse outcome.²⁰ Whether genotyping is able to predict phenotype and/or prognosis on the basis of characterisation of malignant versus benign mutations remains to be established by studies on genotype-phenotype correlations. The role of electrophysiologic study with programmed ventricular stimulation in identifying patients at risk of lethal ventricular arrhythmias is debated. Three recent, separate studies reported different results.

The largest study by Corrado *et al*²¹ reported that the incidence of appropriate ICD discharge did not differ between patients who were and were not inducible at programmed ventricular stimulation for either primary and secondary prevention of arrhythmic sudden death, regardless of indication for ICD implant. In this study, the type of ventricular tachyarrhythmia inducible at the time of electrophysiological study did not appear to predict the occurrence of VF during follow-up. The results of this study indicate that the electrophysiological study is of limited value in identifying patients at risk of lethal ventricular arrhythmias because of a low predictive accuracy (approximately 50% of both false-positive and false-negative results). This finding is in agreement with the limitation of electrophysiological study for arrhythmic risk stratification of other non-ischaemic heart disease such

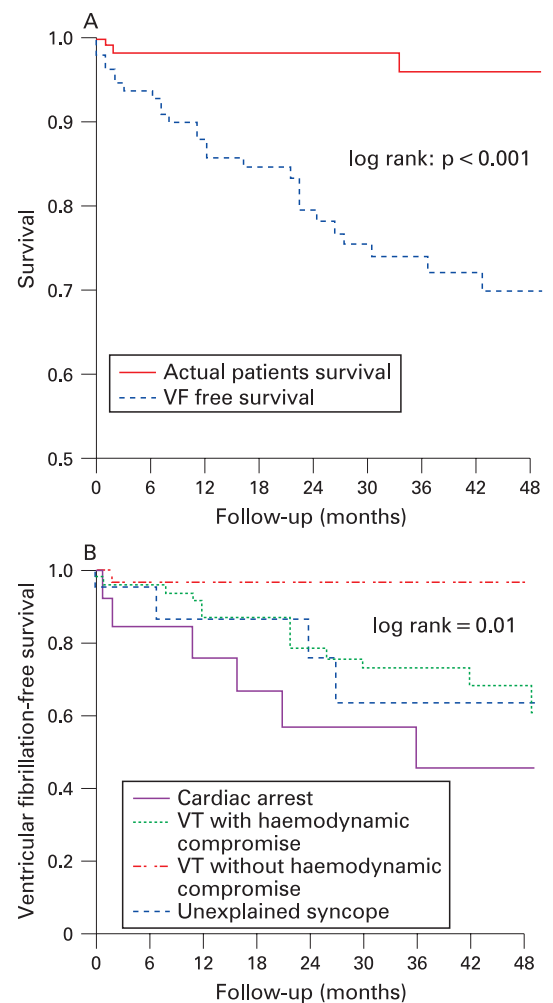


Figure 5 (A) Kaplan-Meier analysis of actual patient survival (upper line) compared with survival free of ventricular fibrillation (VF) (lower line) that in all likelihood would have been fatal in the absence of an implantable cardioverter-defibrillator (ICD). The divergence between the lines reflects the estimated mortality reduction by ICD therapy of 24% at 3 years of follow-up. (B) Kaplan-Meier curves of freedom from ICD interventions on VF for different patient subgroups stratified for clinical presentation. Patients who received an ICD because of sustained ventricular tachycardia (VT) without haemodynamic compromise had a significantly lower incidence of VF during follow-up. Reproduced from Corrado *et al*,¹⁷ with permission of the publisher.

as hypertrophic and dilated cardiomyopathy. In the study by Wichter *et al*,²² in which patients with a history of cardiac arrest or sustained VT were enrolled, inducibility of VT or VF at pre-implant electrophysiological study demonstrated a trend toward statistical significance for subsequent appropriate device interventions. Roguin *et al*²³ reported that VT induction was the most significant independent predictor of appropriate ICD firing in their cohort of ARVC patients. Further studies on a large patient population are needed to establish whether electrophysiological study with programmed ventricular stimulation may identify those ARVC patients, with no prior spontaneous VT or VF, in whom the probability of sudden arrhythmic death is

sufficiently high to warrant an ICD for primary prevention.

Treatment

The first objective of management therapy in patients with ARVC is to prevent sudden death. Therapeutic options include β -blockers, antiarrhythmic drugs, catheter ablation, and ICD therapy. The current data indicate that asymptomatic ARVC patients do not require any prophylactic treatment. They should be followed up on a regular basis by non-invasive cardiac evaluations for early identification of warning symptoms and demonstration of disease progression or ventricular arrhythmias. Importantly, asymptomatic and healthy gene carriers should be prudently advised to refrain from participating in physical exercise and sport activity, which is associated with an increased risk of ventricular arrhythmias and disease worsening. Whether prophylactic β -blockers may reduce the rate of ARVC progression and arrhythmic complications in asymptomatic patients and gene carriers remains to be proven. Antiarrhythmic drug therapy is the first choice treatment for patients with well tolerated and not life threatening ventricular arrhythmias. The available evidence suggests that either sotalol or amiodarone (alone or in combination with β -blockers) are the most effective drugs with a relatively low proarrhythmic risk, although their ability to prevent sudden death has not been proven.

ICD therapy is the most logical therapeutic strategy for patients with ARVC, whose natural history is primarily characterised by the risk of sudden arrhythmic death and, only secondarily, by contractile dysfunction leading to progressive heart failure. The results of published trials strongly suggest an improvement in long term prognosis by ICD therapy in high risk patients with ARVC.^{21–23}

Although ICD confers optimal protection against sudden death, the significant rate of inappropriate interventions and complications, as well as the psychological repercussions mostly in the younger age group, argue strongly against indiscriminate device implantation.

The best candidates for ICD therapy are patients with prior cardiac arrest, VT with haemodynamic compromise, and extensive RV/LV involvement. Unexplained syncope is also considered a predictor of sudden death and appears to be an indication for ICD implantation. In this high risk group of patients the ICD intervention rate is approximately 10% per year and the estimated mortality reduction at 36 months of follow-up ranges from 24–35%^{21–23} (fig 5A). In contrast, patients with well tolerated VT and localised RV myocardial disease appear to have a good long term prognosis (fig 5B). In this subgroup of patients, antiarrhythmic drug therapy (including β -blockers) and/or catheter ablation seem to be a reasonable first line therapy. It is noteworthy that VT relapses are frequently observed after catheter ablation (up to 85% of the cases) and have been attributed to development of new arrhythmogenic zones because of the progressive nature of the underlying heart muscle disease.²⁴ Therefore, catheter ablation is usually reserved for ARVC patients with drug refractory incessant VT or frequent recurrences of VT after ICD implantation, in whom it is the only option available.

In asymptomatic patients and gene carriers there is no general indication for prophylactic ICD implantation, because of their overall favourable prognosis and the high rate of device and electrode related complications observed during follow-up. ICD therapy in patients with multiple risk factors, familial sudden death, or VT/VF inducibility at programmed ventricular stimulation is controversial and the decision to implant should be made on a case-by-case basis.

In patients with RV or biventricular heart failure, treatment consists of diuretics, angiotensin converting enzyme (ACE) inhibitors and digitalis, as well as anticoagulants. Heart transplantation is the final therapeutic option in cases of refractory congestive heart failure and/or untreatable ventricular arrhythmias.

Competing interests: In compliance with EBAC/EACCME guidelines, all authors participating in Education in Heart have disclosed potential conflicts of interest that might cause a bias in the article. The authors have no competing interests.

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- **A review of the current status of knowledge concerning gene mutations that cause ARVC.**
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