

# Arrhythmogenic right ventricular cardiomyopathy

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## Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare condition characterised by ventricular arrhythmias and a specific right (and occasionally left) ventricular pathology. In patients over 35 years of age, coronary artery disease is the leading cause of sudden cardiac death. In younger patients, hypertrophic cardiomyopathy, anomalous coronary arteries and valvular heart disease account for most cases of sudden death.<sup>1,2</sup>

Although previously thought to be very rare, ARVC is being increasingly recognised as a cause of sudden cardiac death, particularly in younger patients. We report here on a family with ARVC and then discuss the condition in more detail.

## Case report

The index case is that of a 33-year-old female who presented in 2000 complaining of palpitations and chest pain. Initial ECG was normal, frequent unimorphic premature ventricular contractions (PVCs) were noted on Holter monitoring and there were frequent ventricular ectopics (left bundle-branch block [LBBB] morphology) before, during and in the recovery phase of a treadmill exercise stress test.

The woman's echocardiogram was normal.  $\beta$ -blockers were commenced and serial Holter monitoring arranged. She had a history of exertional syncope. There was no family history of sudden death. Repeated Holter monitoring revealed non-sustained ventricular tachycardia and a cardiac magnetic resonance imaging (MRI) was performed. MRI findings were consistent with right ventricular cardiomyopathy. An automatic implantable cardioverter defibrillator (ICD) was implanted in February 2003.

Several months later, the patient's 12-year-old daughter presented to A&E with palpitations and dyspnoea. Non-sustained ventricular tachycardia was noted on initial ECG; her echocardiogram was normal, frequent ventricular ectopy was noted before, during and after exercise testing. Cardiac MRI findings were consistent with ARVC.  $\beta$ -blockers and flecainide were commenced with total resolution of symptoms and resolution of ectopy. The patient was advised against partaking

in competitive sports and has regular Holter monitoring. An ICD was not inserted due to her low risk stratification.

Screening of two siblings (17 and 20 years) was arranged. Baseline ECGs showed ventricular ectopy; echocardiograms and cardiac MRI scans were reported as normal, Holter monitoring and exercise testing revealed frequent ventricular ectopy without any evidence of ventricular tachycardia. Neither sibling fulfilled diagnostic criteria for ARVC.

## ARVC

ARVC is distinct from the more familiar forms of cardiomyopathy — dilated, hypertrophic and restrictive. It has three characteristic features:<sup>3</sup>

1. Progressive fibro-fatty replacement of the right ventricular myocardium.
2. Strong familial transmission.
3. Presentation with symptomatic arrhythmias or sudden death at a relatively early stage in the disease.

## Prevalence

Its prevalence is difficult to estimate as many cases are only recognised post-mortem. Cases are often unrecognised because of the lack of diagnostic criteria in the past and lack of effective screening tools. It is an uncommon condition, most reported cases being from the Veneto region of Italy. Whether the disease is truly endemic in this region or is just better understood, screened for and diagnosed more frequently is unknown.

It has a male predominance (2.7:1 ratio) and usually presents in the late 20s and early 30s. The disease almost always occurs after puberty, though it has been detected in persons of all ages.<sup>4</sup>

## Pathophysiology

ARVC is characterised by a progressive loss of myocytes. This is caused by massive or partial replacement of myocardium by fatty or fibro-fatty tissue. Residual strands of myocytes are surrounded by fat or fibrous tissue providing a substrate for electrical instability, leading to sustained ventricular arrhythmias and sudden death.

Two pathological variants have been described. The 'fatty' variant is characterised by transmural infiltration of adipose tissue with sparing of the septum and left ventricle and without wall thinning. In contrast, the 'fibro-fatty' variant is characterised by extensive replacement-type fibrosis, wall thinning, aneurysm formation and left ventricular involvement.<sup>5,6</sup>

### Genetics

Familial ARVC shows a predominantly autosomal-dominant mode of inheritance and incomplete penetrance. An autosomal-recessive form of ARVC associated with palmoplantar keratoderma and woolly hair (Naxos disease) has also been reported. The search for genes responsible for autosomal-dominant ARVC is under way. Gene linkage analysis of large pedigrees has revealed multiple chromosomal loci on chromosomes 3 and 14.

The current hypothesis is that ARVC is a disease of cell adhesion. The identification of mutations in the desmoplakin gene and the cardiac ryanodine receptor gene will undoubtedly provide further insights into the pathogenesis of the disease.

### Disease phases

There are four clinical phases:

- silent phase;
- appearance of arrhythmias;
- appearance of structural abnormalities; and
- onset of heart failure.

The clinical manifestations may vary — from an asymptomatic form with ventricular ectopics to heart failure and sudden death in the young. Symptoms may be due to arrhythmias originating in the affected myocardium, including ectopic beats, ventricular tachycardia and atrial and ventricular fibrillation. Features at presentation include syncope, presyncope, palpitations, ventricular arrhythmias, right and left heart failure and sudden death. In the latter stages of the disease, it is clinically indistinguishable from dilated cardiomyopathy.

The high prevalence of ventricular dysrhythmias and sudden death in this condition is out of proportion to the extent of left ventricular or right ventricular dilation and dysfunction and is an important clue which may suggest the diagnosis. Sudden death is more common in adolescents and young adults and, importantly, may be precipitated by exertion.<sup>7</sup>

Table 1		
	Major	Minor
Global/regional dysfunction and structural alterations (imaging techniques)	Severe right ventricular (RV) dilation. Decrease in RV ejection fraction (EF) with normal left ventricular (LV) function. RV localised aneurysms. Severe RV segmental dilation.	Mild global RV dilation +/- decrease RV EF with normal LV EF. Mild RV segmental dilation. Regional RV hypokinesia.
Tissue characterisation of the RV myocardium	Fatty infiltration of the RV myocardium.	
Repolarisation abnormalities		Inverted T waves in V2-V3 (if age >12 years, in the absence of right bundle branch block).
Depolarisation/conduction abnormalities	Global/regional dysfunction and structural alterations.	Late potentials.
Arrhythmias		Sustained/non-sustained ventricular tachycardia with LBBB morphology. Frequent ventricular ectopics (>1,000/24 hours).
Family history	Family history with anatomic confirmation (autopsy, surgery).	Sudden death in <35 years, with suspicion of ARVC. Family history of ARVC (clinical diagnosis).

## Diagnosis

The diagnosis is based on the detection of structural, histological, electrocardiographic, arrhythmic and genetic factors. It is based on major and minor criteria as set out by the European Society of Cardiology task force. The diagnosis is made when the patient presents with two major criteria, one major and two minor criteria or four minor criteria (see Table 1).

Major criteria include severe dilation and reduction of right ventricular ejection fraction +/- impairment of left ventricular systolic function, localised right ventricular aneurysms, severe segmental dilation of the right ventricle and fatty infiltration on cardiac MRI. Minor criteria include mild global right ventricular dilation +/- reduction in right ventricular systolic function with normal left ventricular systolic function, mild segmental dilation of the right ventricle and regional right ventricular hypokinesia, also ECG findings of Epsilon waves or a quasi-random signal (QRS) duration of >110ms in V1-4.

ECG is a useful initial diagnostic test, though a normal ECG does not exclude the diagnosis. The most frequent ECG abnormalities include:

- 1 T wave inversion in V1-4;
2. conduction delays through the right ventricle;
- 3 PVCs with LBBB morphology and superior axis; and
4. ventricular post-excitation waves (Epsilon waves).

## Treatment

There is no curative treatment. The aim is to detect patients at high risk and prevent sudden death. Anti-arrhythmics are the first line of treatment and standard anti-failure treatment should be instituted following the development of heart failure.

Catheter ablation may be of use for dysrhythmias refractory to drug treatment. ICDs are the most effective treatment option in 'at risk' patients. Cardiac transplant surgery is considered in severe biventricular failure with recurrent ventricular arrhythmias.

## Risk stratification

The main objective of risk stratification is to prevent arrhythmic sudden death. Risk factors that have emerged from retrospective clinical and pathological series include young age at diagnosis, family history of sudden death, history of cardiac arrest, extensive right ventricular disease, left ventricular involvement, syncope and presence of ventricular arrhythmias.

## Conclusion

ARVC is a recognised cause of sudden death, especially in young people. A high index of suspicion is needed in susceptible patients. Diagnosis should be made as per task force criteria. Prevention of sudden death is the aim of treatment. Screening of family members of index cases is imperative.

## References

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