Original Article

Guidelines for the Diagnosis and Management of Arrhythmogenic Right Ventricular Cardiomyopathy

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Background: **Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an uncommon inherited myocardial disorder characterised by fibro-fatty inflammation affecting the right and left ventricles. It most commonly presents with palpitations or syncope but sudden death may occur, especially in young males.**

Methods: **Diagnosis is not possible with a single test and may be difficult. Task Force criteria agreed in 1994 comprise major and minor criteria spanning structural abnormalities, ECG appearances, arrhythmias, family history of premature death and myocardial histology. Modified criteria were introduced in 2010 to improve sensitivity.**

Results: **Arrhythmogenic right ventricular cardiomyopathy is a desmosomal disease. Mutations have been detected in five desmosomal genes, most frequently in plakophilin-2 (PKP2) and multiple mutations are also reported. Antiarrhythmic drugs such as sotalol and amiodarone may improve symptoms but are unproven to increase survival. An implantable defibrillator is appropriate in individuals surviving cardiac arrest or sustained ventricular tachycardia, but there is not yet consensus about prophylactic treatment of Task Force positive but asymptomatic individuals.**

Conclusions: **Arrhythmogenic right ventricular cardiomyopathy is more common than previously believed. Preliminary evidence supports improved sensitivity without loss of specificity using the revised Task Force criteria. The genetics of the disease are complex but should ultimately advance diagnosis and management.**

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Keywords. Arrythmias, cardiac; Arrythmogenic right ventricular cardiomyopathy/dysplasia; Death, sudden, cardiac; Diagnosis; Echocardiography; Magnetic resonance imaging

Clinical Characteristics

Definition and Prevalence

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myocardial disorder characterised by fibro-fatty inflammation affecting both the right ventricle (RV) and left ventricle (LV) with a wide phenotypic expression. Its true prevalence is unknown, with estimates of between 1 in 2000 and 1 in 5000. Our concepts of the disease continue to evolve in parallel with wider recognition of the condition and genetic analysis (currently incomplete).

Clinical Presentation

Arrhythmogenic right ventricular cardiomyopathy most commonly presents with palpitations, nonsustained ventricular tachycardia (VT) and syncope, but many patients are initially asymptomatic. Symptoms correlate poorly with disease severity. The onset of symptoms is usually between 20 and 40 years of age, but cases can occur in childhood and a RV aneurysm has been observed in a 27 week-old foetus. The male:female ratio is about 3:1 at presentation, but in genotyped cohorts the sex ratio is unity. Sudden death may be the presenting symptom, especially in young males, but is uncommon in diagnosed patients. Whilst the clinical course is progressive, the rate is very variable. Conventionally four stages have been described (latent, symptomatic ventricular arrhythmias of RV origin, isolated right heart failure, dilated biventricular cardiomyopathy) but recent studies employing late enhancement magnetic resonance support a biventricular pathology in most patients from the outset. Certain regions of the right ventricle are classically affected, the so-called triangle of dysplasia (outflow tract, apex, sub-tricuspid area). Arrhythmogenic right ventricular cardiomyopathy has been unusually prominent as a cause of death in young athletes in Italy, with a particular concentration in the Veneto region. There is strong evidence that ARVC is a desmosomal disease, and this would accord with the thinner walled RV initially showing morphologic change, especially in athletes or other individuals with high exercise levels in whom there is some evidence that symptoms and sudden death present at a younger age. Knowledge of

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Table 1. *Task Force Criteria for ARVC Diagnosis.*

	Major Criteria	Minor Criteria
Structural and functional abnormalities	1. Severe dilation and reduction of RVEF with mild or no LV involvement 2. Localised RV aneurysm (akinetic or dyskinetic areas with diastolic bulging) 3. Severe segmental RV dilation	1. Mild global RV dilation and/or reduction with normal LV 2. Regional RV hypokinesis
Tissue characterisation	Infiltration of RV by fat with presence of surviving strands of cardiomyocytes	
ECG depolarisation/conduction abnormalities	1. Localised QRS complex duration $\geq$110 ms in V1, V2, or V3 2. Epsilon wave in V1, V2, or V3	Late potentials on signal-averaged ECG
ECG repolarisation abnormalities		Inverted T-waves in right precordial leads (in V1 through V3 above age 12, in the absence of RBBB)
Arrhythmias		1. LBBB VT (sustained or non-sustained) on ECG, Holter, or ETT 2. Frequent PVCs (>1000/24 h on Holter)
Family history	Family history of ARVC confirmed by biopsy or autopsy	1. Family history of premature sudden death (<age 35) due to suspected ARVC 2. Family history of clinical diagnosis based on present criteria

Source: Adapted from McKenna, WJ, et al., Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy, Br Heart J 1994;71:215–8.
ETT, exercise stress test; PVCs, premature ventricular contractions; RVEF, right ventricular ejection fraction.

the responsible genetic mutations is presently incomplete and their relation to the phenotype is likely complex.

Clinical Diagnosis

Unfortunately ARVC cannot be diagnosed by a single test as, for example, echocardiography for hypertrophic cardiomyopathy. The Task Force criteria (see below) agreed in 1994 are very helpful but lack sensitivity for affected family members and possibly asymptomatic younger people at increased risk of sudden death. Recently, a proposed modification of the Task Force criteria has been published which will likely improve sensitivity [5]. These modified guidelines are more prescriptive for defining morphologic RV changes with separate criteria for echocardiographic and MRI assessments. They are not, in the interests of space, presented here in full, but importantly, new major criteria have been proposed. They include an RV ejection fraction $\leq$ 40% on MRI, nonsustained or sustained VT of LBBB morphology and superior axis, a pathologic mutation associated or probably associated with ARVC and the presence of T wave inversion in right precordial leads has been upgraded from minor to major. The threshold for significant ventricular ectopy on Holter monitoring has also been lowered from >1000/24 h to 500/24 h. Although more time will be necessary to fully assess the impact of these changes, McKenna's group have reported a significant increased sensitivity using the new criteria. The combination of two major, a major and two minor or four minor criteria remain required for the diagnosis (Table 1).

Morphologic assessment of the RV is hampered by its architecture and an inadequate knowledge of the limits of normality, so that subtle early changes are easily missed. Focussed echocardiography can help make the diagnosis with particular emphasis on RV outflow tract measurements and RV systolic function assessment. In addition, there are qualitative features such as localised apical or subtricuspid valve aneurysms and hypertrabeculation. The preferred imaging modality is magnetic resonance (MRI) and the modified Task Force criteria are more precise in what constitutes minor and major abnormalities. The ability to demonstrate late enhancement with MRI scanning has been an advance and has increased detection of LV involvement, although no provision for this information is presently included in the modified guidelines. Biplane ventricular angiography may also be helpful, but a careful technique is necessary for adequate imaging. The only imaging modality at present that can comment on tissue characterisation is MRI. However, there are concerns that fatty infiltration can be overinterpreted and could lead to an overdiagnosis of ARVC. Abnormal histology can contribute a major criterion, but many histopathologists lack sufficient experience to make a confident interpretation. Recently, immunohistochemical analysis of an endomyocardial biopsy sample [1] was reported as a possibly highly sensitive and specific diagnostic test for ARVC. Interestingly plakoglobin signal levels were reduced in normal-appearing LV as well as areas showing typical fibrofatty change in the RV. Unfortunately ongoing work suggests this finding may be similarly present in dilated cardiomyopathy so that its specificity and clinical value remain to be determined.

Late potentials may be detected by signal-averaged ECG but their overt presence as an epsilon wave on the surface ECG is probably a late feature. T wave inversion in the right precordial leads correlates with RV enlargement and fibro-fatty infiltration and similar inversion in the lateral or inferior leads seems to correlate with LV involvement. Using the old Task Force criteria the diagnosis is often strongly suspected but not proven; it remains to be seen how the newer version will perform [6]. Familial involvement occurs in more than 50%, but unexpected deaths in family members older than 35 years do not qualify as a minor criterion.