The Cardiac Society of Australia and New Zealand

Guidelines for the diagnosis and management of Arrhythmogenic Right Ventricular Cardiomyopathy

The development of these guidelines was co-ordinated by Dr Warren Smith and members of the CSANZ Cardiovascular Genetic Diseases Writing Group.

The guidelines were reviewed by the Continuing Education and Recertification Committee and ratified at the CSANZ Board meeting held on Friday, 15th April 2011.

1. Clinical Characteristics

1.1 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).

1.2 Clinical presentation

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

1.3 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. 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 ≤ 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. More time will be necessary to assess the impact and utility of these changes. The combination of two major, a major and two minor or four minor criteria remain required for the diagnosis.

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. Localized 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 Characterization	Infiltration of RV by fat with presence of surviving strands of cardiomyocytes	
ECG Depolarization/ Conduction Abnormalities	1. Localized QRS complex duration >110 msec in V1, V2, or V3 2. Epsilon wave in V1, V2, or V3	Late potentials on signal-averaged ECG
ECG Repolarization 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 hours 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

ETT, Exercise stress test; PVCs, premature ventricular contractions; RVEF, right ventricular ejection fraction.

Source: Adapted from W.J McKenna et al., Diagnosis of arrhythmogenic right ventricular dysplasia/dardiomyopathy, Brit Heart J 1994;71:215-8.

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 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. Familial involvement occurs in more than 50%, but unexpected deaths in family members older than 35 years do not qualify as a minor criterion. Modified Task Force criteria (one minor criterion only) have been proposed, but not universally accepted for family members with a diagnosed proband.

2. Molecular Genetics

Genetic screening is commercially available but remains predominantly confined to research laboratories. Five desmosomal genes are associated with ARVC; plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein (DSG-2), desmocollin (DSC2), and plakoglobin (JUP). Inheritance is autosomal dominant unless otherwise specified. Multiple mutations have been reported to be associated with an increased risk of sudden death. Identification of a pathogenic mutation categorised as associated or probably associated with ARVC has now been assigned major criterion status in the revised criteria.

Plakophilin-2 (*PKP2*): mutations have been reported in 6-43% of Task Force-positive patients, with penetrance among mutation carriers reported to be nearly 50%. Patients carrying *PKP2* mutations present at an earlier age than those without mutations and the arrhythmia-free survival is lower.

Desmoglein-2 (*DSG2*) and Desmocollin-2 (*DSC2*): mutations have been predominantly associated with predominantly left ventricular involvement.

Desmoplakin (*DSP*): mutations have been identified in two autosomal recessive syndromes (Carvajal and a "Naxos like" syndrome) and in some patients in the North American ARVC Registry. It is hypothesized that desmoplakin mutations predispose to early left ventricular involvement from disruption of cytoskeletal integrity.

Plakoglobin (*JUP*): homozygous mutations are associated with Naxos disease, an autosomal recessive condition characterised by palmo-plantar hyperkeratosis and woolly hair. Heterozygous plakophilin-deficicient mice that underwent 8 weeks of daily swimming developed premature right ventricular enlargement and dysfunction (but not fatty infiltration).

The transmembrane gene *TMEM43* has been implicated in ARVD5 in Newfoundland families and affected males have a median survival of 41 compared to 83 years in mutation-free individuals. Affected males are also three times more likely to develop heart failure. In a few families mutations have been described in transforming growth factor beta 3 (*TGF-B3*) and cardiac ryanodine receptor (*RYR2*) genes, but their significance seems presently marginal.

3. Management

3.1 Affected individuals

Exercise: Strenuous exercise (e.g. basketball, squash, skiing, soccer, singles tennis, cycling, running and windsurfing) is strongly recommended to be avoided. There is a plausible (but unproven) explanation as to why such exercise might be deleterious with the thinner walled right ventricle more vulnerable to cellular disruption.

Antiarrhythmic drugs/ICD: Beta-blockers, sotalol and amiodarone have been the most commonly used antiarrhythmic agents. There are no data however that drug treatment improves survival in the absence of sustained ventricular arrhythmias, so that the real management issue is the timing and indications for an implantable defibrillator (ICD). There is consensus that cardiac arrest survivors or patients with sustained VT should have an ICD. The indications for primary prevention are more controversial. There is a groundswell that patients meeting Task Force criteria should also be offered an ICD, regardless of the presence of documented ventricular arrhythmias. Prophylactic ICD implantation in a Newfoundland population (ARVC5) recorded a 5-year cumulative frequency for first appropriate discharge of 70%. On the debit side is the relatively poor long-term survival of present leads (annual failure rates up to 20% by 10 years) imposing multiple leads and the hazard of possible lead extraction in younger implanted patients. At present therefore, asymptomatic patients need to be managed on a case-by-case basis, with a low threshold in the presence of a family history of premature death.

Radiofrequency ablation: Ablation is moderately successful for ventricular tachycardia when antiarrhythmic drugs are inadequate or not tolerated, but recurrence rates are higher than for outflow tract VT because of the generalised nature of the disease and combined ICD treatment is necessary regardless of outcome. Occasional patients will come to cardiac transplantation either because of intractable arrhythmias or heart failure.

3.2 Asymptomatic family members

Both a 12-lead and, if possible, a signal-averaged ECG should be obtained on all first-degree relatives. Because of the relative insensitivity of echo, MRI scanning is also recommended for adults and older children beginning age 10-12 years when general anaesthesia is no longer necessary. Screening should be repeated every 5 years until age 30, and once more at age 40. After age 40 coronary artery disease is a greater risk for sudden death and history and ECG will suffice in hitherto normal individuals. If the MRI is minimally abnormal (mild segmental or global enlargement) the scan should be repeated after 3 years, with reversion to 5 yearly thereafter if no further interval change. The presence of intramyocardial fat by itself may be normal, but congruent late enhancement suggests pathology. In younger children, an ECG and an echocardiogram at 3 yearly intervals is recommended until MRI without anaesthesia is feasible. Genetic screening should be undertaken where possible, but caution is warranted in concluding mutation-free individuals are necessarily at low risk until more data are available.

3.3 Genetic counselling

There is presently insufficient information on which to confidently advise patients on the basis of presently identified mutations. However genetic testing should be encouraged where the opportunity for analysis exists, to expand our knowledge base and the opportunity for genotype-phenotype correlation. Notwithstanding the potential for sudden death in a minority, it is important to emphasize that most diagnosed patients can lead full and normal lives.

4. Further Information

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