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Editorial

Arrhythmogenic Right Ventricular Cardiomyopathy: From Diagnosis to Treatment

Gregory Dendramis[1]*, M.D.

[1]*Cardiovascular Division, University Hospital "Paolo Giaccone", Palermo, Italy*

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***Corresponding author**

Gregory Dendramis, C.da S.Caterina, snc, CAP 90037, Piana degli Albanesi, Palermo, Italy, Email: gregorydendramis@libero.it

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Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia (ARVC) is a genetic form of cardiomyopathy affecting primarily the Right Ventricle (RV) but also may involves the Left Ventricle (LV) and may culminate in life-threatening ventricular arrhythmias, Sudden Cardiac Death (SCD) and/or heart failure. In most cases it is transmitted with an autosomal dominant pattern of inheritance, with incomplete penetrance and variable expression, but there are also some rare autosomal recessive forms as Naxos disease and Carvajal syndrome.

The term "cardiomyopathy" should be preferred to "dysplasia", as already suggested by WHO/International Society and Federation of Cardiology in 1996 and Maron, about classification of cardiomyopathy in 2006 [1,2].

The estimated prevalence of ARVC in the general population is approximately 1:5000, affecting men more frequently than women with a ratio of 3:1 [3,4] and accounts for 11%-22% of cases of SCD in young athletes, resulting in approximately 22% of cases in athletes in northern Italy and about 17% of SCD in young people in the United States [5-7].

The pathologic hallmark of disease is myocardial atrophy (myocyte loss), fibrofatty replacement, fibrosis and ultimate thinning of the wall with chamber dilation and aneurysm formation [8]. The genetics of ARVC support the hypothesis that it may be caused by desmosomal dysfunction (mutation of plakophilin-2, desmoglein-2, desmocollin-2, desmoplakin genes) that lead to impaired mechanical and electrical coupling between individual cells, leading to myocyte uncoupling, especially under conditions that increase myocardial strain, for example during physical effort [9]. These changes may produce electrical instability precipitating ventricular tachycardia and SCD.

Currently only approximately 50% of probands are found to have a pathogenic mutation, possibly due to the high incidence of rare mutations in many patients and actually the most important utility of genetic test are in the screening of asymptomatic family members of probands who have a pathologic genetic abnormality [9].

Diagnosis of ARVC relies on a scoring system, formulated in 2010 by the revisited Task Force, with major and minor criteria based on the demonstration of a combination of defects in RV morphology and function, characteristic depolarization/repolarization electrocardiogram abnormalities (negative T waves and/or "epsilon" wave in right precordial leads), characteristic tissue pathology, typical arrhythmias, family history, and the results of genetic.

Patients are diagnosed as having definite ARVC if they have "4 points" with major criteria equal to 2 points and minor criteria equal to 1 point. Patients whose score totals to "3 points" can be classified as having probable ARVC [9].

Assessment of ventricular structure and function is critical for the diagnosis and prognosis of ARVC. Transthoracic echocardiography provides a noninvasive method of RV imaging, suggestive findings of ARVC include global or segmental wall motion abnormalities (akinesis/dyskinesis) with cavity dilation, hypertrophic RV trabeculation, and systolic dysfunction [9], (Figure), (Table).

To date Cardiac magnetic resonance (MRI) is considered the best imaging modality in evaluating the RV in ARVC and provides tissue characterization and identification of intramyocardial fat and fibrosis (Delayed Enhancement, DE-MRI) in addition to assessment of ventricular structure and function [10,11]. Endmyocardial biopsy has low diagnostic sensitivity for several reasons as the patchy distribution of the disease and the high rate of sampling errors [9].

Symptoms usually appear between the ages of 30-50 and the most common clinical presentation consists of palpitations, syncope and ventricular tachycardia of left bundle branch morphology, especially in young patients [12]. In cases of older patients in whom the disease has been described, the clinical presentation is mainly represented by signs and symptoms of right or biventricular heart failure [13].

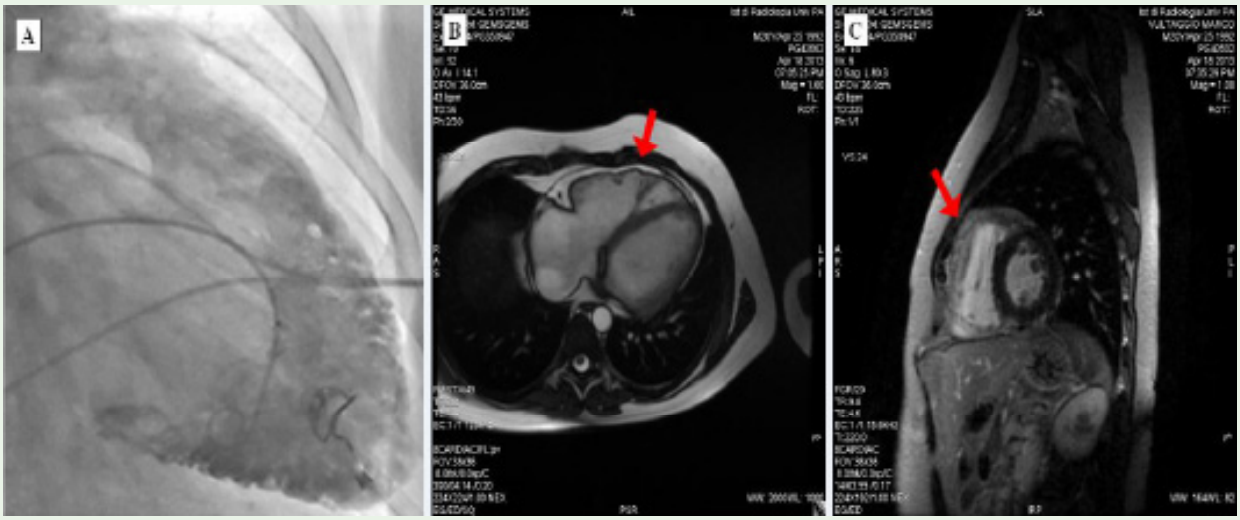

Figure 1: ARVD: ventriculography (panel A) and cardiac magnetic resonance with areas of dyskinesia of the RV free wall (panel B) and parietal signal alterations (panel C).

Table 1: 2010 Task Force Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy.

I. Global and/or regional dysfunction and structural alterations	
Major	- By 2-dimensional echocardiogram: regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32mm (corrected for body size [PLAX/BSA] ≥19mm/m2), PSAX RVOT ≥36mm (corrected for body size [PSAX/BSA] ≥21mm/m2), Fractional area change ≤33%.
	- By MRI: regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110mL/m2 (male) or ≥100mL/m2 (female), RV ejection fraction ≤40%.
	- By RV angiography: regional RV akinesia, dyskinesia, or aneurysm.
Minor	- By 2-dimensional echocardiogram: regional RV akinesia or dyskinesia and 1 of the following (end diastole): PLAX RVOT ≥29 to <32mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m2), PSAX RVOT ≥32 to <36mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m2), Fractional area change >33% to ≤40%.
	- By MRI: regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2 (female), RV ejection fraction >40% to ≤45%.
II. Tissue characterisation of the wall	
Major	- 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.
Minor	- Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.
III. Repolarisation abnormalities	
Major	- Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120 ms).
Minor	- Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete RBBB) or in V4, V5, or V6Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete RBBB.
IV. Depolarisation/conduction abnormalities	
Major	- Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3).
Minor	- Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110ms on the standard ECG: filtered QRS duration (fQRS) ≥114 ms; duration of terminal QRS <40μV (low-amplitude signal duration) ≥38 ms; root-mean-square voltage of terminal 40 ms ≤20μVTerminal activation duration of QRS ≥55ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete RBBB.
V. Arrhythmias	
Major	- Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL).
Minor	- Nonsustained or sustained ventricular tachycardia of RVOT configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis >500 ventricular extrasystoles per 24h (Holter).
VI. Family history	
Major	- ARVC confirmed in a first-degree relative who meets current Task Force criteria. - 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.
Minor	- History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria. - Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative. - ARVC confirmed pathologically or by current Task Force criteria in second-degree relative.

ARVC, Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia; aVF, augmented Voltage unipolar left Foot lead; aVL, augmented Voltage unipolar Left arm lead; BSA, Body Surface Area; ECG, Electro Cardio Gram; LBBB, Left Bundle Branch Block; MRI, Magnetic Resonance Imaging; PLAX, Parasternal Long-Axis view; PSAX, Parasternal Short-Axis view; RBBB, Right Bundle Branch Block; RV, Right Ventricular; RVOT, Right Ventricular Outflow Tract; SAECG, Signal-Averaged ECG.

The main goal of therapy is to prevent life-threatening events. To achieve this it is necessary to identify high-risk patients for malignant arrhythmias and SCD that should be considered for ICD implantation in primary prevention. Consequently patients with unexplained syncope, non-sustained VT on noninvasive monitoring, familial history of sudden death, extensive disease including those with LV involvement and good functional status are potential candidates for ICD implantation even in the absence of ventricular arrhythmias. ICD implantation in secondary prevention is obviously mandatory [10,14]. To date VT ablation has an ancillary role and may be helpful in reducing symptoms and ICD firing but not able to prevent SCD [14,15].

Antiarrhythmic drugs, primarily beta blockers, sotalol, and amiodarone have been used for symptomatic control in patients who are not candidates for ICD or as an adjunct therapy to reduce frequent ICD firing due to recurrent VT, but the evidence available has been derived from observational studies [15,20]. Finally, but not least, an important recommendation for patients with ARVC is exercise restriction because an intense physical activity appears to increase the rate of progression of the disease [21,22].

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