The Pharma Innovation Journal 2017; 6(2): 169-171

www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2017; 6(2): 169-171

www.thepharmajournal.com
Received: 25-12-2016
Accepted: 26-01-2017

Sergiy Fedorov
Ivano-Frankivsk National Medical University, Ukraine

Correspondence
Sergiy Fedorov
Ivano-Frankivsk National Medical University, Ukraine

The main aspects of treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia

Sergiy Fedorov

Abstract
Arrhythmogenic right ventricular dysplasia is a cause of sudden death in young people and athletes. The purpose of this study was to review of modern aspects of management of arrhythmogenic right ventricular dysplasia. Pharmacological options in ARVD treatment consist of antiarrhythmic agents, beta-blockers, and heart failure drug therapy. Implantable defibrillator therapy is the most logical therapeutic strategy for patients with ARVC/D, because the natural history is primarily characterized by the risk of SCD and, only secondarily, by contractile dysfunction leading to progressive heart failure.

Keywords: Arrhythmogenic right ventricular cardiomyopathy/dysplasia, treatment, cardiomyopathy

1. Introduction
Arrhythmogenic right ventricular dysplasia (ARVD) is a genetically determined myocardial disease characterised by fibrous fatty replacement and ventricular arrhythmias, involving the right ventricle predominantly, starting at the epicardium and extending transmurally [1]. It is a rare inherited heart-muscle disease that is a cause of sudden death in young people and athletes. The prevalence of ARVD in the general population is difficult to estimate due to the challenging nature of the diagnosis. Studies in Europe report a prevalence of between 0.6 and 4.4 per 1000, but these may be biased by geographic variation in clinical and pathological expertise. This disease is reported as a cause of sudden cardiac death in 11%-27% of individuals aged ≤35 years [2].
ARVD is considered to be familial with autosomal dominant inheritance, although there are recessive forms (eg, Naxos disease, Carvajal syndrome) that are associated with a cutaneous phenotype [3]. Seven genes have been identified that are associated with this disease: plakoglobin (*JUP*), desmoplakin (*DSP*), plakophilin-2 (*PKP2*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), transforming growth factor beta-3 (*TGFβ3*), and *TMEM43* [4]. Mutations in RYR2 coding the ryanodine receptor have been reported in ARVC/D in patients with an arrhythmic presentation (stress-induced bidirectional ventricular tachycardia) in the absence of significant electrocardiographic or structural abnormalities.
It has been suggested that patients with ARVC/D may be predisposed or susceptible to viral myocarditis, which could lead to a decrease in cardiac function and accelerate progression of the disease [5]. The link between ARVC/D and myocarditis is still undefined.
The purpose of this study was to review of modern aspects of management of arrhythmogenic right ventricular dysplasia.

2. Results and Discussion
The concept of a specific right ventricle cardiomyopathy was first suggested in a report of six patients with sustained ventricular tachycardia (VT) and enlarged right ventricles published in 1977. In 1982, the term “arrhythmogenic right ventricular dysplasia” was first used in a case series of 24 patients with left bundle branch block (LBBB) pattern VT, right ventricle wall motion abnormalities and replacement of the right ventricle myocardium by adipose and fibrous tissue [2]. However, arrhythmogenic right ventricular dysplasia (or as it was later renamed, arrhythmogenic right ventricle cardiomyopathy) was not formally recognized as a distinct entity until 1994, following the publication of diagnostic criteria by the World Health Organization/International Society and Federation of Cardiology Task Force [6]. But in 2010 the new diagnostic criteria were proposed [7].
The basic scheme (table 1), and the diagnostic terminology are following:

- Definite diagnosis: two major, or one major and two minor or four minor criteria from different diagnostic categories.

- Borderline diagnosis: one major and one minor or three minor criteria from different diagnostic categories.
- Possible diagnosis: one major or two minor criteria from different diagnostic categories [7].

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]≥19 mm/m^2)• PSAX RVOT≥ 36mm (corrected for body size [PSAX/BSA]≥21 mm/m^2)• O 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≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)• O 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/m^2)• PSAX RVOT≥32 to <36mm (corrected for body size [PSAX/BSA]≥18 to <21 mm/m^2)• O 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/m^2 (male) or ≥90 to <100 mL/m^2 (female)• Or 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 (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS≥120 ms)
Minor	Inverted T waves in leads V_1 and V_2 in individuals>14 years of age (in the absence of complete RBBB) or in V_4, V_5, or V_6. Inverted T waves in leads V_1, V_2, V_3, and V_4 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 (V_1 to V_3)
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 V_1, V_2, or V_3, 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/D confirmed in a first-degree relative who meets current Task Force criteriaARVC/D confirmed pathologically at autopsy or surgery in a first-degree relativeIdentification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteriaPremature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relativeARVC/D confirmed pathologically or by current Task Force criteria in second-degree relative

Notes: ARVC/D - arrhythmogenic right ventricular cardiomyopathy/dysplasia; aVF - augmented voltage unipolar left foot lead; aVL - augmented voltage unipolar left arm lead; BSA - body surface area; ECG - electrocardiogram; 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 ventricle; RVOT - right ventricular outflow tract; SAECG - signal-averaged electrocardiogram.

Clinical presentations in patients with ARVD vary widely. Heart failure, ventricular arrhythmias and sudden cardiac death (SCD) are the most severe clinical manifestations of this disease.

The most important objectives of clinical management of ARVD patients include: (i) reduction of mortality, either by arrhythmic SCD or death from heart failure; (ii) prevention of disease progression leading to RV, LV, or biventricular dysfunction and heart failure; (iii) improvement of symptoms and quality of life by reducing/abolishing palpitations, VT recurrences, or ICD discharges (either appropriate or inappropriate); and (iv) limiting heart failure symptoms and increasing functional capacity. Therapeutic options consist of lifestyle changes, pharmacological treatment, catheter ablation, ICD, and heart transplantation [8].

It is recommended that patients with a definite diagnosis of ARVD not participate in competitive and/ or endurance sports [8].

Pharmacological options in ARVD treatment consist of antiarrhythmic agents, beta-blockers, and heart failure drug therapy.

Antiarrhythmic agents are recommended as an adjunct therapy to ICD in ARVD patients with frequent appropriate device discharges. The available evidence suggests that amiodarone (loading dose of 400–600 mg daily for 3 weeks and then maintenance dose of 200–400 mg daily), alone or in combination with beta-blockers, is the most effective drug for preventing symptomatic ventricular arrhythmias with a relatively low proarrhythmic risk even in patients with ventricular dysfunction, although its ability to prevent SCD is unproved [9].

Beta-blocker therapy is recommended in ARVD patients with recurrent VT, appropriate ICD therapies, or inappropriate ICD interventions resulting from sinus tachycardia,

supraventricular tachycardia, or atrial fibrillation/flutter with high-ventricular rate [8].

Catheter ablation is a therapeutic option for ARVD patients who have VT. Fibrofatty replacement of RV myocardium creates scar regions that are regarded as arrhythmogenic substrate for VT. Ventricular tachycardia is the result of a scar-related macro-reentry circuit, similar to that observed in the post-myocardial infarction setting, which is suitable for mapping and interruption by catheter ablation. Catheter ablation may be guided by either conventional electrophysiological or substrate-based mapping during sinus rhythm [10].

Implantable defibrillator therapy is the most logical therapeutic strategy for patients with ARVD, because the natural history is primarily characterized by the risk of SCD and, only secondarily, by contractile dysfunction leading to progressive heart failure. Prospective randomized trials are currently not available for ethical reasons and because of practical limitations predominantly linked to relatively low disease prevalence and low event rate. The available data, coming from observational studies/registries of large populations of ARVD patients, have established efficacy and safety of ICD therapy [8].

Heart transplantation is recommended as a final therapeutic option in ARVD patients with either severe, unresponsive congestive heart failure or recurrent episodes of VT/VF which are refractory to catheter (and surgical) ablation in experienced centres and/or ICD therapy.

3. Conclusion

Arrhythmogenic right ventricular dysplasia is a cause of sudden death in young people and athletes. Current therapeutic and preventive measures are palliative, not curative. The future investigation in management of it will be based on the discovery of the molecular mechanisms that are involved in the aetiology and pathogenesis of the disease.

4. References

1. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. The Lancet. 2009; 373:1289-1300.
2. Quarta G, Elliott PM. Diagnostic criteria for Arrhythmogenic right ventricular cardiomyopathy. Rev. Espa. Cardiol. 2012; 65:599-605.
3. Protonotarios N, Tsatsopoulou A, Anastasakis A, Sevdalis E. Genotype-phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. J Am Coll Cardiol. 2001; 38:1477–1484.
4. Marcus FI, McKenna WJ, Sherrill D, Basso C. Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. Circulation. 2010; 121:1533-1541.
5. Calabrese F, Angelini A, Thiene G, Basso C, Nava A, Valente M. No detection of enteroviral genome in the myocardium of patients with arrhythmogenic right ventricular cardiomyopathy. J Clin Pathol. 2000; 53:382-387.
6. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G *et al*. Diagnosis of arrhythmogenic right ventricular dysplasia / cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994; 71:215-8.
7. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA *et al*. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force criteria. Eur Heart J 2010; 31:806-14.
8. Corrado D, Wichter T, Link MS. Treatment of arrhythmogenic right ventricular dysplasia / cardiomyopathy: an international task force consensus statement. Eur Heart J. 2015; 36(46):3227-3237.
9. Marcus GM, Glidden DV, Polonsky B. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol. 2009; 54:609-615.
10. Philips B, Madhavan S, James C. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Arrhythm Electrophysiol. 2012; 5:499-505.