

Arrhythmogenic Right Ventricular Dysplasia, Did We Know Everything

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ABSTRACT

Arrhythmogenic right ventricular dysplasia is a cardiomyopathy of the young that presents with a sudden cardiac death. It has unique features that prompted a different classification, based on a combination of right ventricular imaging by echocardiography and cardiac magnetic resonance imaging, histology, repolarization abnormalities, depolarization and conduction abnormalities, arrhythmias and family history (including genetic testing). Hence the usual investigative pathway requires a multimodality approach. Treatment is complex and starts with exercise restriction in this young active population and ends up with insertion of an Automated

Implantable Cardioverter Defibrillator with its own morbidity. Antiarrhythmic drugs eliminate frequent episodes of ventricular tachycardia and defibrillator shocks but is not a curative therapy. There has been a great progress in studying the underlying role of genetics but the field is still wide open. This review will focus on the recent updates in arrhythmogenic right ventricular dysplasia pathology and treatment.

Key words: Arrhythmogenic right ventricular dysplasia; Classification; Echocardiography; Genetic

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INTRODUCTION

Arrhythmogenic right ventricular dysplasia (ARVD) is a rare type of cardiomyopathy that was first clinically described in 1982. It is also known as arrhythmogenic right ventricular cardiomyopathy, right ventricular cardiomyopathy or right ventricular dysplasia. ARVD has a prevalence of 1: 1000-1: 5000 with male predominance^[1]. This condition is more commonly found in individuals of Italian and Greek descent.

ARVD is an inherited heart muscle disease characterized by myocardial atrophy and fibrofatty replacement of the ventricular myocardium. Fatty deposition might occur up to 17% normally and increase with age-focal macroscopic fat deposition. This results in two distinct phases known as concealed and electrical phase. Fibrofatty replacement of RV myocardium is also known as an isolated or associated lesion with left ventricle involvement.

The pathophysiology is complex and warrants close investigation of the interaction between genetic mutations and exposure to physical activity.

The symptoms are usually exertional by the age of thirty and the most dramatic is Sudden Cardiac Death in athletes, accounting for up to 20% of deaths, making ARVD-the second most common cause af-

ter hypertrophic cardiomyopathy in young people < 35 years of age. Syncope, palpitation, and lightheadedness are common symptoms^[2].

Physical examination is unremarkable except in the presence of accompanied syndrome like Naxoz is a special form of ARVD, inherited as a recessive transmission with a familial penetrance of 90%. It is characterized by ventricular arrhythmias with ventricular extra-systoles and tachycardia in the presence of features of severe histologic changes and marked RV dilatation in the presence of non-cardiac features in the form of skin thickening of the hands and soles of the feet and a predisposition to woolly hair. The first responsible gene was located on chromosome 17, and its product plakoglobin^[3].

CLASSIFICATION

The exact diagnosis was standardized in 1994 by the international task force where major and minor criteria were identified in six categories: right ventricular imaging (including echocardiography and cardiac magnetic resonance imaging (MRI)), histology, repolarization abnormalities, depolarization and conduction abnormalities, arrhythmias and family history (including genetic testing). Combining the findings of different diagnostic modalities can establish a “definite”, “borderline” or “possible” diagnosis of ARVD.

Patients were grouped into four categories: “definite,” “borderline,” “possible,” and “none” ARVD. Definite will be diagnosed with two major criteria or one major and two minor or four minor. It was specific but not sensitive^[4].

In 2010 a new guideline was proposed that was based on global or regional dysfunction and structural alterations. On echo the major criteria were regional RV kinesis, dyskinesia or aneurysm plus one of the following: RVOT > 32 mm (index > 19 mm/m²) in PS long or 36 mm (index > 21 mm/m²) in parasternal short or FAC < 33%. Lower values than above were suggested and considered to be minor.

The major criteria in MRI were RV kinesis, dyskinesia or dyssynchronous contraction plus one of the following: RVEDV index > 110 ml/m² or RVEF < 40%. Lower values than above were suggested and considered to be minor.

Similar structural changes as described above in RV angiography were also considered major criteria^[5].

Some experts suggest future iterations to improve the revised criteria, e.g. enhanced imaging protocols able to detect subtle changes in RV structure and function, or incorporation of electro-anatomical data, response to adrenergic challenge, and validated criteria for interpreting genetic variants^[6].

In addition, the revised criteria should be used with caution in children and adolescents suspected of ARVD. A positive result in 12-Lead ECG, CMR and echo should prompt genetic testing. Gene mutations of desmoplakin or plakophilin loci have highly positive with high negative predictive value in detecting definite ARVD^[7]. Genetic testing plays an important role not only in diagnosis but also in screening of family members.

Analysis of large population sequencing data has demonstrated higher than expected frequency of ARVD variants suggesting that a proportion of ARVD has reduced penetrance of some variants, and/or a polygenic etiology of ARVD. The five commonly mutated genes were PKP2, DSP, DSG2, DSC2 and JUP, accounting for half of ARVD cases. Applying minor allele frequency increases the penetrance where ARVD-causing variants may be inaccurately classified^[8].

The incidence of pathological or likely pathological desmosomal mutations in ARVD is very high, with most mutations causing

truncation. However, the presence of desmosomal mutations did not affect the prognosis^[9].

INVESTIGATION

Unfortunately no gold standard test to diagnose ARVD is available and multiple diagnostic information needs to be added^[10].

In ECG, Epsilon waves are hallmark features, reflect significant RVOT involvement, which is associated with episodes of sustained ventricular tachycardia but not sudden cardiac death^[11].

The distribution of RV voltage abnormalities can be predicted by region-specific ECG depolarization changes in patients with ARVD and ventricular tachycardia. QRS fragmentation during and/or immediately after the QRS complex in ≥ 2 contiguous ECG leads are frequently observed in patients with ARVD and reflect delayed conduction and/or RV endocardial and epicardial electroanatomic maps due to RV fibrosis^[12]. Fragmented QRS (frQRS) complex, with various morphology has recently been rdescribed as a diagnostic criterion of ARVD and predicts fatal and nonfatal arrhythmic events^[13].

While abnormal electroanatomic mapping areas were proportionate to the extent of inverted T wave, abnormal voltage might exist without repolarization change. More advanced transmural disease is noted with down sloping elevated ST-segment pattern in V₁ and V₂ representing a more unipolar endocardial voltage abnormality^[14]. Positioning ECG electrodes at a high anterior position improves the identification of ARVD, as well as increasing P wave amplitude, while multichannel ECG recordings add little to the reliability of diagnosing ARVD^[15].

Stimulation with certain drugs e.g. isopternlol was also reported to improve diagnosis^[16].

Echocardiography is the major diagnostic tool. Its sensitivity peaked if combined with MRI^[13], but other echo-based techniques might also help e.g. RV deformation. In screening of the relatives of patients with ARVD, a normal subtricuspid region deformation is associated with absence of disease progression during 4-year follow up. Abnormal RV deformation seems to precede the established signs of ARVD^[17]. The sensitivity was also reported to be higher with intracardiac ultrasound detecting RV aneurysm^[18]. One of the major advantages of MRI has been to reveal left dominant ARVD, a variant that is not addressed in the diagnostic criteria and missed clinically due to the focus on RV^[19].

Myocardial biopsy is usually diagnostic. Perforation risk at the RV free wall cannot be neglected^[21-21].

It is important to consider mimickers of ARVD. Congenital absence of pericardium reported to have ECG, chest X-ray, and echo findings of ARVD. Cardiac MRI can confirm such a diagnosis. Another differential diagnosis would be cardiac sarcoidosis that might present with arrhythmia. Athletes’ hearts rarely cause a challenge in ruling out ARVD as it induces physiological changes detectable on electrocardiography and imaging which may overlap with pathological findings of ARVD^[22-23].

TREATMENT

Exercise restriction is critical in affected individuals and at-risk family members. Competitive or endurance exercise is known to accelerate progression of ARVD.

Antiarrhythmic drugs and ventricular tachycardia ablation including endocardial and epicardial approaches are valuable but are palliative components of the management. Ablation is potentially an

effective strategy for eliminating frequent VT episodes and AICD shocks rather than a curative therapy.

AICD in high-risk patients is the only therapy that provides adequate protection against sudden death. However, patient selection is challenging but important because of device-related complications and inappropriate shock. In one study, complications occurred in 21% participants, 21% had inappropriate ICD interventions; overall mortality was low at 2%^[24].

Ventricular tachycardia at presentation, inducible on EPS study, male sex, inverted T waves in ≥ 3 precordial leads and PVC $\geq 1000/24$ hours were predictors for appropriate AICD therapy. After multivariable analysis, the only predictor was induction on electrophysiology study^[25].

Some research added the presence of multiple mutations or a mutation in TMEM43 to be taken into consideration when determining arrhythmic risk^[26].

In advanced stages of ARVD, cardiac transplantation is advised, which is performed predominantly due to heart failure. Age under 35 years at first symptoms was independently predictor. Survival was 91% at 5 years after transplant^[27,28,1].

ARVD has been reported during pregnancy, it is associated with a low rate of major cardiac events during pregnancy and vaginal delivery appears safe. A higher number of pregnancies did not seem to relate to a worse phenotype ARVD in women. The risk of sustained ventricular arrhythmia seems poorly predictable and major cardiac events were frequent in childhood, supporting the need to continue beta-blockers during pregnancy and close cardiac monitoring^[29-30].

It is important not to focus on VT as the sole contributor to syncope and death in patients with ARVD, as pulmonary embolism has been reported to occur as well the absence of VT with typical LBBB morphology especially when the right heart is extremely enlarged^[31].

CONCLUSION

ARVD is a disease of the young with well identified criteria that becomes more recognizable with advances in cardiac imaging but still presents challenges as to the best mode of treatment.

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