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Review Article

Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia

Marçalo J[1], Falcão LM[1,2]*

[1]Department of Cardiology, University Hospital Santa Maria, Centro Hospitalar Lisboa Norte (CHLN), Portugal

[2]Department of Cardiology, University of Lisbon, Portugal

***Corresponding author:** Luiz Menezes Falcão, University Hospital Santa Maria, Centro Hospitalar Lisboa Norte (CHLN), Lisboa, Portugal / University of Lisbon, Faculty of Medicine, Lisbon, Portugal

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Abstract

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) is an under diagnosed idiopathic progressive cardiomyopathy, associated with mutations in genes coding for desmosomal proteins, with well-studied hereditary mechanisms in some populations. The Task Force 2010 defined diagnostic criteria for ARVC/D: structural (by echocardiography and cardiac magnetic resonance imaging); histopathological (if biopsy is required); electrical (by electrocardiography, exercise testing and Holter monitoring) and genetic/ familial. When those criteria are met, the associated sudden death risk should be then tackled by EPS, leading to the eventual insertion of an Implantable Cardioverter Defibrillator. Genetic association studies should be offered to ARVC/D patient's offspring.

Keywords: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; Transthoracic echocardiography; Magnetic resonance imaging; Cardiac sudden death; Cardiac electrophysiologic study; Implantable cardioverter defibrillator

Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) is a progressive heart muscle disease, of unknown aetiology, with well-studied hereditary transmission in some population subgroups. It is characteristically associated with gene mutations of desmosomal myocardial proteins (plakoglobin, desmoplakin, plakophilin-2, desmoglein-2 and desmocollin-2, etc.) conditioning abnormalities in the intercellular adhesion of myocytes with its subsequent fibrofatty tissue replacement, which results in gradual changes of the ventricular wall - thinning and hypokinesis/ dyskinesis which may progress to dilatation of the affected cavity, most commonly the right ventricle. It is an under-diagnosed clinical entity due to the nonspecific nature of its presentation that is typically characterized by tachycardia and ventricular dysfunction, as well as increased risk of sudden cardiac death [1-5].

Based on Task Force 2010 (TF 2010) regarding ARVC/D diagnosis, structural/functional criteria are followed (normally evaluated through echocardiography and magnetic resonance), as well as histopathological (if endomyorcardial biopsy is chosen), electrical (by electrocardiography, exercise testing and Holter monitor) and genetic/familial [1]. Frequently, the risk of sudden cardiac death is evaluated by electrophysiological studies, which can lead to the inserting of an Implantable Cardioverter Defibrillator (ICD). Studies of genetic association should be offered to the patient's offspring [2].

Epidemiology

Epidemiological data related with this disease are not extensively available. It is estimated that ARVC/D prevalence in general population may vary between 1/2000 and 1/5000, with men being more affected than women (3:1). Its incidence varies from approximately 1/1000 to 1/50.000, due to the strongly variable geographical distribution [3-5].

ARVC/D diagnosis is made in most cases (80%) before the age of 40. On a worldwide basis, in young adults, ARVC/D is the cause of sudden cardiac death in 5-11% of the total number of cases. On a study carried out in the northern region of Italy, ARVC/D was the main cause of sudden death in young adults, particularly, athletes (22,4% of total cases) [6].

ARVC/D should be therefore considered in young individuals who first present with a history of arrhythmia, syncope or cardiorespiratory arrest, and seldom as the first episode in older age individuals. A late diagnosis becomes even more difficult due to the existence of possible confounding factors, such as concomitant coronary heart disease [7].

Biopathology

Data from electron microscopy point to changes in desmosomal proteins as the main ultrastructural factor that triggers failure in the adhesion of myocytes [8], resulting in cell death and progressive fibrofatty tissue replacement, which is the classical pathological hallmark of ARVC/D. These structural changes will cause an additional mechanical stress to the ventricular myocardium, with focal dilatation of the cavity, in an early stage located in the thinner areas of the Right Ventricle (RV) - (apex, inflow tract, outflow tract - "triangle of dysplasia") - and later affecting all of its extension. In fact, this model can explain the development, in early stages, of RV tropism, it being more distensible, thinner and more asymmetrical than the Left Ventricle (LV) [9].

However, LV involvement is very common (>50%) and its prevalence increases with aging and progression of the disease. A study with 42 patients with ARVC/D showed that 76% had left ventricle involvement, with evidence of fibrofatty degeneration in post-mortem samples or after cardiac transplantation. Furthermore, there are cases in which LV involvement is the dominant aspect and the ultimate expression of the disease can be similar to that of dilated cardiomyopathy [10-12].

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A connection between physical exercise and progression of disease has been identified, which supports the model that links mechanical stress with this cardiomyopathy, explains the early and more severe form of disease in athletes, favouring the indication for restricting exercise in affected patients. In an early stage of the disease, structural changes are confined to the "triangle of dysplasia" and the patient is asymptomatic, while being at risk of sudden death, mainly during exercise. Subsequently, myocardial fibers in the fibroadiposal zones are the substrate for development of symptomatic ventricular arrhythmias and functional changes in the RV become apparent [10].

Genetics

There has been great variability in studies regarding the percentage of inherited cases of ARVC/D, with data varying between 30% and more than 50%.

In a sample of 439 ARVC/D diagnosed individuals, according to TF 2010, mutations were identified in around 276 - 63% of affected people. The same study showed that the presence of mutations in relatives correlates with the expression of the disease - ARVC/D diagnosis in relatives with identified mutation was twice as frequent (40% *vs*. 18%). However, it should be emphasized that in a large proportion of patients no mutations or family history were identified [3,13].

The main desmosomal proteins whose changes are associated with ARVC/D are plakoglobin, desmoplakin, plakophilin-2, desmoglein-2 and desmocollin-2. Other genes have already been identified, such as TMEM 43 protein (associated with a type of high risk ARVC/D, which seems to be related to the lipogenic pathway regulated by PPAR- γ), TGF-β3 gene and cardiac ryanodine receptor gene (RYR2) - which pathogenic mechanisms that lead to ARVC/D are still under study. Other mutations that may be associated with the phenotype of ARVC/D are not yet clear [1,14,15]. Two patterns of inheritance have been identified more commonly, autosomal dominant forms of incomplete penetrance and autosomal recessive forms in which the ARVC/D is part of a syndrome that includes palmoplantar keratoderma and woolly hair (Naxos Disease and Carvajal Syndrome associated with plakoglobin and desmoplakin genes, respectively) [16,17]. Due to the pattern of incomplete penetrance, age of onset of symptoms and clinical manifestations can vary within individuals with the same mutation. For that reason, it is important to identify asymptomatic carriers in risk of developing the disease at a given time [9,18].

Natural History and Clinical Manifestations

The natural history of ARVC/D displays a correlation between the degree of RV dysfunction progression and the development of symptoms. The initial presentation is wide, from palpitations, dizziness, malaise, chest pain and dyspnea, to syncope, and, less frequently, sudden death. The onset of symptoms usually happens between the first and fifth decades of life, with 30 years old being the average age of diagnosis. It rarely occurs before 12 and after 60 years old. Symptoms such as palpitations and syncope may be the manifestation of ventricular arrhythmias, which can range from frequent ventricular extrasystoles to sustained ventricular tachycardia, with the frequency of arrhythmic events being proportional to the severity of the disease. In a follow-up study of 130 ARVC/D diagnosed patients, the most common symptoms were: palpitations - 66,9%, syncope - 32,3%, atypical chest pain - 26,9%, dyspnea - 10,8 % and clinical signs of right ventricular failure - 6,2%. The remaining 6.2 % were asymptomatic [3,9,15].

This condition can remain clinically silent for decades. In macro and microscopic post-autopsy heart examinations from 1930 cases of sudden cardiac death with no identified cause, around 10% showed evidence of ARVC/D. The overall mortality rate lies between 4-20 %, for both genders, with a peak in the fourth decade of life. The annual rate of sudden death in patients with this condition is 1% [19,20]. Due to high mortality rates, risk of sudden cardiac death and knowing that ARVC/D is a progressive disease, diagnosis and treatment should be prompt, which is not always the case, especially in sporadic cases with no recognized family history [21].

Diagnostic Approach

No diagnostic method alone is conclusive and sufficient, particularly in the early stages of the disease. The two essential diagnostic tools, when first suspecting ARVC/D, are Electrocardiography (ECG) and Transthoracic Echocardiography (TTE) [22].

ECG

In suspected cases of ARVC/D, ECG should always be part of the initial diagnostic approach. ECG changes are observed in about 90% of affected patients [4]. Despite the low sensitivity of ECG (40-50% in the first episode), long-term ECG monitoring showed high sensitivity and specificity. The most important electrocardiographic findings in patients with ARVC/D are changes in ventricular repolarization - inversion of T wave in V1 -V3 being the most frequent (54-100 % of patients). This change, although part of the major criteria of TF 2010 for diagnosis of ARVC/D, is not specific to this condition, and may be observed in healthy individuals. The epsilon wave is the most specific finding of ARVC/D. It is present in 30% of cases and corresponds to the delay in the electrical stimulation of the RV. Other findings are complete or incomplete right bundle branch block and extension of the terminal portion of QRS [23].

The association between ECG findings and the risk of sudden death, cardiac arrest, heart transplant, ventricular fibrillation, sustained ventricular tachycardia, and arrhythmic syncope was evaluated in 111 patients with ARVC/D. T-wave inversion in the inferior leads, extension and dispersion of the QRS interval duration were important predictors of these events. Electrocardiographic changes follow the gradual course of the disease, with evidence of temporal progression of ECG changes in up to 89% of observed individuals [30].

Echocardiography

TTE is the most used method to detect functional and structural heart changes. It is non-invasive and easily accessible in most hospital centres [3,4,18]. However, due to the retrosternal position of the RV and its complex geometry, use of TTE as the sole imaging method is problematic [24]. The most commonly identified changes are: RV dilatation, especially of the outlet chamber, where regional aneurysms and atria dilatation can occur; morphological irregularities - that occur in up to 62% of those affected - such as trabecular disorganization and a moderator band with increased reflectivity; decreased right ventricular fractional area change (RVFAC) - which correlates with

the ejection fraction. Regional RV wall motion changes are observed in 80% of cases [25].

Echocardiographic measurements currently included in TF2010 diagnostic criteria are not considered as reliable (less sensitive) as those of Cardiac Magnetic Resonance (CMR), mainly due to difficulties in evaluating ventricular wall regional motion disorders. New three-dimensional echocardiography techniques aim to overcome these limitations. Some studies showed that, in addition to the diagnostic value of echocardiography, it also exhibits a prognostic value in ARVC/D. It was found that the decrease in Tricuspid Annular Plane Systolic Excursion (TAPSE) and RVFAC are associated with major cardiac events. However, as referred above, major arrhythmic events may occur before the existence of systolic dysfunction. Therefore, risk stratification is hampered by the wide variability in phenotypic expression of the disease [24].

Cardiac magnetic resonance imaging

As previously observed, echocardiography is not always sufficient for diagnosis of ARVC/D and magnetic resonance imaging overcomes some of its limitations. The CMR is a non-invasive method used to detect infiltration of adipose tissue in the myocardium, wall thinning and regional wall motion changes. Common CMR findings used for the diagnosis of ARVC/D are: presence of hyperintense areas in ventricular wall (which indicates fat deposition), dilatation of the right atrium, RV and its outflow tract, and hypokinesia/akinesia/dyskinesia [26].

A CMR method that seems to have good connection with the histopathology and with the degree of right ventricular dysfunction and Ventricular Tachycardia (VT) induction in the electrophysiological study is the delayed enhancement after paramagnetic contrast injection, used to detect fibrous tissue. This technique was positive in 67% of patients with ARVC/D [27].

Some studies have shown that CMR has a better diagnostic value in ARVC/D, compared with the conventional echocardiography [22,28]. However, it is also subject to false positive results, especially if the used criteria are strictly based on the fibro-adipose changes and ventricular wall thickness [18,24,29]. It has been found, in some populations, that around 50% of apparently healthy elderly subjects had fat infiltration in the ventricular wall. An assessment made in 46 patients who were considered to have ARVC/D, using only the method of fat infiltration and ventricular wall narrowing by CMR, showed that no individual met the criteria for ARVC/D according to TF 2010.

In addition to the percentage of false positives, some CMR limitations are related with the inter-observer interpretation variability, the existence of artefacts related to arrhythmogenic phenomena, the limited use in the presence of intracardiac devices, its cost and accessibility in less differentiated hospital centres [30].

CT-Angio

Almost the same changes as in CMR can be identified with this technique. It may be preferred where image quality is not sufficient and in the presence of cardiac arrhythmias. Additionally, it is one of the chosen methods in the presence of some intracardiac devices [18].

Right ventricular angiography

With a specificity of 90%, the RV angiography could be considered the "gold standard" in the diagnosis of ARVC/D. However, because of its invasive nature and associated complications, it is not used as the first line in the diagnosis of this entity, having been replaced by CRM. The findings are the presence of hypertrophic trabeculae with deep fissures, prominent moderator band and regional aneurysms. However, it can be used when the diagnosis is not conclusive by other methods, or when endomyocardial biopsy considered [18].

Holter electrocardiographic monitoring

Several studies have shown the importance of Holter monitor in ARVC/D, not only to identify premature ventricular extrasystoles, but also to find life threatening ventricular arrhythmias, with a correlation being found between the two conditions [31-33].

Electrophysiological study

There are conflicting data regarding a scheduled ventricular stimulation and the induction of ventricular tachycardia in ARVC/D risk stratification. However, the later, while not predictive of future arrhythmic events, can identify patients at a high risk of disease progression and sudden death [34].

In a follow-up study of 62 patients diagnosed with ARVC/D by TF 2010 criteria, 55% had inducible monomorphic ventricular tachycardia. After ten years observing these patients, they had a higher prevalence of cardiac-cause death, heart transplant, ventricular fibrillation and ventricular tachycardia with hemodynamic instability [18,35].

The International Task Force Consensus of July 2015 recommends the electrophysiological study in the diagnosis and/or evaluation of suspected ARVC/D cases (Class IIa) [36].

Genetic testing

The use of genetic tests is not advocated for all patients with suspected ARVC/D, particularly in patients whose diagnosis was based on the TF 2010 criteria.

It can be useful when clinical, electrocardiographic and imaging results are dubious but the diagnosis remains plausible (Class IIb) [37].

With the identification of previously mentioned TMEM 43 protein gene, a new window of opportunity has opened for genetic testing, concerning risk stratification, as this gene seems to be associated with a mortality rate of 50% in men up to 39 years old [38].

Endomyocardial biopsy

Biopsy will be diagnostic when <60% of myocytes are identified in the right ventricle free wall, with fibrous tissue replacement, with or without fatty tissue. The segmental nature of histopathological involvement and the risk of perforation - particularly at the level of the free wall, which results in interventricular septum often being biopsied (although it is frequently not affected) - limit its use in the presence of other non-invasive methods. Therefore, cardiac biopsy is not recommended in first evaluation of ARVC/D [18].

Diagnosis and Risk Stratification

The main causes for incorrect diagnosis of ARVC/D are

misinterpretation of CMR and the lack of knowledge regarding TF 2010 criteria. A study of imaging techniques performance referred that only 50% of patients diagnosed with ARVC/D by CMR met the echocardiographic criteria of TF 2010, which highlights the importance of CMR in the approach of this pathology [39].

Search for risk stratification indicators showed that RV and LV dysfunction, presence of TMEM 43 protein gene mutation, T-wave inversion in left of V3 leads and the presence of sustained ventricular tachycardia are the most solid contenders. Given the progressive nature of the disease, risk stratification should be considered as a dynamic process subject to temporal re-evaluation [34].

Therapeutic Approach

The therapeutic strategy should always be focused, on a first approach, in the prevention of sudden cardiac death, although the best way to prevent this dramatic outcome is not yet well defined. Current guidelines promote secondary prevention by using ICD in patients with ventricular tachycardia or fibrillation, and as primary prevention in high-risk patients (young age, athletes, substantial family history and frequent episodes of syncope). Because of the above mentioned reasons, restriction of exercise is mandatory for patients with ARVC/D. Therefore, they should not regularly participate in high competition sports (Class Ic) [36,40,41].

Antiarrhythmic drugs

There is still poor evidence of drug efficacy in the prevention of arrhythmic phenomena. Regarding beta-blockers, despite few specific studies for ARVC/D, their importance is induced from the knowledge of its protective effects in patients without ARVC/D, particularly regarding sudden cardiac death risk. Hence, their use is recommended (class Ic) [12].

More studies should be carried out in order to confirm the effectiveness of these and other drugs in primary prevention in ARVC/D gene carriers [36,42,43].

Implantable Cardioverter-Defibrillator (ICD)

Current recommendations agree on the importance of ICD's implantation in patients who meet the TF 2010 criteria, particularly in the presence of family history of sudden cardiac death, sustained ventricular tachycardia or recent unexplained syncope. The number of premature ventricular systoles has shown to be proportional to the suitability of the ICD and to frequency of arrhythmic events. The inducibility of ventricular tachydysrhythmia on EPS proved to be a predictor of ICD adequacy [9,12]. As primary prevention, ICD should be an option in high-risk patients, even without consensus on its determinants. Syncope showed a predictive relationship with ICD appropriate interventions in patients with prophylactic implantation of this device, namely the prevention of life-threatening events [44,45]. As secondary prevention, it should be an option in the presence of documented VT or VF [44,46,47]. The main complications related to ICD implantation include pocket hematoma, problems related to the position of electrodes, as well as pericardial effusion and infection. Particularly, in patients with ARVC/D, perforation of the RV wall can occur, as well as structural changes, which adversely affects the placement of ICD electrodes and may interfere with the sensitivity and heart rate. Furthermore, the ICD in young individuals needs to be replaced and the electrodes eventually relocated in the future [48].

Radiofrequency ablation

Due the segmental distribution and progressive evolution, radiofrequency ablation usually doesn't constitute a definitive treatment and shouldn't be used in isolation as a first-line treatment. In some cases, when the arrhythmogenic focus is well defined, the patients can benefit from this technique. Ultimately, it can decrease the necessity of an ICD [49].

Family Members Monitoring

Genetic studies should be used in detection and risk stratification in asymptomatic family members of patients. However, the presence of mutation does not assure that there will be a clinical expression, it only demonstrates the presence of risk. It should be highlighted that some studies showed that, in cases of familial ARVC/D, 50% of relatives initially unaffected have later developed the disease [2,50,51].

Conclusion

The frequency of malignant arrhythmias as the first ARVC/D indicator stresses the importance of clinical awareness towards signs and symptoms that may suggest the diagnosis and the importance of an early imaging screening. Future goals will be focused on delaying disease progression or even on its reversion. Although not without some risks, multiple studies have shown that ICD is an overall safe therapy in primary and secondary prevention of sudden cardiac death.

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